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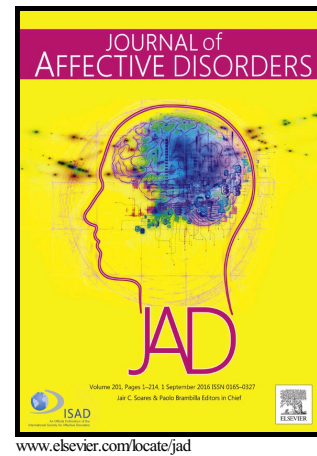
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# Author's Accepted Manuscript

A systematic review of the associations between maternal nutritional biomarkers and depression and/or anxiety during pregnancy and postpartum

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# **A systematic review of the associations between maternal nutritional biomarkers and depression and/or anxiety during pregnancy and postpartum**

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## **Abstract**

### **Background**

Nutritional requirements need to be met in order to adapt to pre- and postnatal changes. Our aim was to systematically review the evidence of associations between nutritional biomarkers and psychological distress during pregnancy and in the first postnatal year.

### **Methods**

MEDLINE, EMBASE, PsycINFO, Scielo, LILACS, clinicaltrials.gov, International Clinical Trials Registry, Cochrane Library, Scopus and Web of Science databases were searched for articles from inception to 4/15/2016. Studies of maternal nutritional biomarkers in blood (fatty acids/micronutrients/amino acids) and associations with psychological distress

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<sup>1</sup> Joint senior authorships

(depression/anxiety/stress) were included. Two independent reviewers extracted data based on study designs, participants, outcomes, exposures, and association measures.

## Results

Thirty-eight studies were included. A total of 13 studies showed divergent or no associations between serum/plasma/erythrocyte fatty acid concentrations and depression/anxiety during pregnancy and postpartum. Changes in serum cholesterol levels from pregnancy to postpartum showed a significant inverse correlation with depression in one out of three studies. Five out of seven studies found an inverse association between serum vitamin D levels and pre- and postnatal depression. Plasma tryptophan levels were inversely correlated with postnatal depression scores in three out of four studies. We identified that one out of two studies presented no significant association between vitamin B<sub>12</sub>/folate/ferritin concentrations and depression in postpartum.

## Limitations

There was higher variability between association measures, time and scales of depression and anxiety assessments.

## Conclusions

The majority of high-quality studies suggest that lower vitamin D levels may be associated with postpartum depression. However, further evidence is needed for guiding clinical practice on nutritional biomarkers.

**Key words:** nutritional biomarker, postpartum, pregnancy, depression, anxiety, stress

## Introduction

Maternal psychological distress is currently defined as depression, anxiety and stress during pregnancy or postpartum. The overall pooled perinatal depression prevalence estimate was

11.9% (95% CI 11.4 - 12.5). The prevalence varied depending on whether cases were self-reported or diagnosed using tools, the time of pregnancy/postpartum, and the income level of the country (Woody et al., 2017). The pooled self-reported symptoms and clinical diagnosis prevalence for anxiety combined with pregnancy as a whole were 22.9% (95% CI 20.5 - 25.2) and 15.2% (95% CI 9.0 - 21.4), respectively (Dennis et al., 2017). For postpartum anxiety, the pooled prevalence varied from 9.3% (95% CI 5.5 - 13.1) to 17.8% (95% CI 13.9 - 21.6) and also depended on the time of postpartum and the screening/diagnostic instrument used (Dennis et al., 2017). Furthermore, evidence suggests that prenatal depression has adverse effects on childhood neurodevelopment and is associated with a higher risk of preterm birth and low birth weight (Accortt et al., 2015; Grote et al., 2010). Similar associations have been observed between anxiety and these adverse obstetric outcomes (Ding et al., 2014). Postnatal depression was found to be associated negatively with cognitive development in toddlers and affects the whole family due to its effects on fathers, the parenting relationship and children's health (Kingston et al., 2015; Letourneau et al., 2012). Psychological distress in mothers has been related to poor nutrition (Barker et al., 2013; Fowles et al., 2011), inadequate prenatal medical care, smoking and alcohol use (Zuckerman et al., 1989).

The development of maternal depression in pregnancy and postpartum has been associated with several factors, among them, socioeconomic deprivation, lack of social support, stressful life events, domestic violence and preconception and/or pregnancy history of mental health problems (Fisher et al., 2012; Lancaster et al., 2010; Patton et al., 2015; Robertson et al., 2004). It deserves to be mentioned that factors such as hormones (i.e., corticotropin-releasing hormone), inflammatory cytokines (i.e., interleukin-6) and genes (i.e., serotonin transporter gene) are involved in the risk of the development of postpartum depression (Yim et al., 2015). Moreover, poor quality and unhealthy diets have also been positively associated with

antenatal depressive and stress symptoms (Baskin et al., 2015). In contrast, a healthy diet was associated with a decrease in antenatal depression and anxiety symptoms (Baskin et al., 2015). However, evidence from one systematic review found conflicting associations across studies between a healthy diet and postnatal depression symptoms (Baskin et al., 2015). Quirk et al. (Quirk et al., 2013) concluded that the evidence of associations between diet quality and dietary patterns and the likelihood of depression was still insufficient. Lai et al. (Lai et al., 2014) reported that a healthy dietary pattern (characterized by a high intake of fruit, vegetables, fish and whole grains) was associated with reduced odds of depression in a meta-analysis with high variability among studies ( $n = 13$  studies, OR = 0.84; 95% CI 0.76 - 0.92;  $I^2 = 81.8\%$ ,  $p < 0.001$ ) conducted in a non-pregnant adult population. The evidence reported among studies in these reviews (Baskin et al., 2015; Lai et al., 2014; Quirk et al., 2013) includes differences in sampling characteristics, timing of assessments during pregnancy or the postpartum period, and tools used to measure psychological distress and dietary quality/dietary intake. Specifically, dietary quality/dietary intake assessments do not produce accurate information, and the main reasons for this are related to the following: food-composition tables, food combinations, and cooking methods.

Several nutritional changes are required to adapt to the physiological, social and emotional alterations that occur during pregnancy and the postpartum period (Baskin et al., 2015; Bodnar and Wisner, 2005). These nutritional changes can be assessed using dietary intake methods. However, these methods do not provide adequate information for assessment if nutritional requirements are being met. In contrast, nutritional biomarkers indicate a more precise and integrated measurement of nutrient intake and metabolism (Potischman and Freudenheim, 2003).

These important metabolites play a critical role in mental health physiology by acting in the biosynthesis and metabolism of hormones and neurotransmitters of the neurotransmission

system, and producing changes in the membranes of neural tissue (Kaplan et al., 2007; Leung and Kaplan, 2009; Rechenberg and Humphries, 2013).

Therefore, it is important to determine the role of maternal nutritional status, assessed by biomarkers, in prenatal and postnatal psychological distress, and in that way, avoid the possible bias introduced by dietary intake assessments. The aim of this systematic review was to evaluate the current evidence regarding the associations between maternal nutritional biomarkers and psychological distress during pregnancy and within the first postnatal year.

## **Methods**

### **Literature Search**

This systematic review followed the PRISMA and MOOSE guidelines (Moher et al., 2009; Stroup et al., 2000). The study protocol was registered in the PROSPERO databases of systematic review ([www.crd.york.ac.uk](http://www.crd.york.ac.uk); registration number CRD42015018990). We performed a comprehensive search of the following electronic databases: Ovid database (MEDLINE, EMBASE, PsycINFO), Scielo, LILACS, [clinicaltrials.gov](http://clinicaltrials.gov), International Clinical Trials Registry Platform (WHO), the Cochrane Library, Scopus and Web of Science from inception up to the 15<sup>th</sup> of April of 2016. A combination of Medical Subject Heading (MeSH) terms and/or text keywords was used and adapted to each database (the PubMed search strategy is presented in Supplementary Table 1). After all records were organized and duplicates were excluded, two independent investigators (Dr. JT and MSc JL) screened titles and abstracts. The full-text articles were retrieved and screened for inclusion according to the eligibility criteria from a list of potential eligible records based on titles and abstracts (see below). Moreover, we screened the references lists of the included studies and relevant reviews, hand-searched key journals and used forward citation tracking of the included studies to identify additional relevant studies. Disagreements on eligibility for inclusion were

resolved by discussion until a consensus was reached between the investigators; a third reviewer (MSc MCV) was consulted twice.

### **Selection Criteria**

The PICOS (participants, intervention, comparison, outcome and study design) criteria used are presented in Table 1. The included studies were required to meet the following criteria: (1) performed in women during pregnancy and/or within the first postnatal year; (2) included measurements of maternal nutritional biomarkers, such as fatty acids, micronutrients (vitamins and minerals) and amino acids in blood (or its fractions); (3) assessed psychological distress, such as depression, anxiety and psychological stress, and diagnosed them using symptom questionnaires, screening measures and/or diagnostic assessments; (4) included one of the following study designs: prospective cohort, cross-sectional, case-control (nested case-control and case-cohort) and baseline of intervention studies; and (5) provided statistical and/or epidemiological association measures. Studies were excluded if outcomes were assessed only by medication use (such as the use of an antidepressant to diagnose a case of depression without a symptom questionnaire, screening measure and/or diagnostic assessment) or if the patient had other evaluated mental disorders (e.g., bipolar disorder) or physiological stress (not being a psychological evaluation).

No restrictions were made on publication date. Only studies published in English, Portuguese and Spanish were considered for inclusion.

### **Data Collection**

Two independent investigators (Dr. JT and MSc JL) performed data abstraction using a structured form. Any discrepancies were resolved by consensus between the investigators. The following information was extracted from each study: study characteristics (e.g., study



design, data, country and sample size), participant characteristics (e.g., age, body mass index and inclusion/exclusion criteria), assessment of maternal distress (e.g., type of distress and assessment), assessment of nutritional biomarkers (e.g., type of biological sample and assessment), results (overall frequencies/means of biomarker and mental disorders, measures of association, list of adjusting variables) and funding sources.

Tables were constructed to summarize the data. For studies reporting statistical and epidemiological associations, the more complete measure of variability was presented (95% confidence interval or *p*-value). When means and standard deviations were reported stratified by groups in the study (such as depressed vs. non-depressed participants for cohort or cross-sectional studies), they were transformed and reported as a single value describing the total sample (Higgins and Green, 2011).

### **Quality Assessment**

The quality of the studies was assessed by two independent investigators (Drs. JT and FR) using the Newcastle-Ottawa Scale (Wells et al., 2012). Any disagreements were discussed between the investigators until a consensus was reached. The Newcastle-Ottawa scale evaluates the following domains: participant selection, comparability of groups, and ascertainment of the outcome or exposure. The scale gives a maximum of one or two points on each item depending on the domains, and the maximum total number of points for all domains is equal to nine. Studies with total scores from 0-3, 4-6 and 7-9 were considered low, moderate and high quality, respectively. Furthermore, for the quality assessment graphical representation of each item of each domain, studies were considered of high methodological quality if they received the maximum number of points for the item in the specific domain and of low quality if they did not. The methodological quality graph representation was depicted as a percentage of the number studies with high, moderate and

low quality in each item of the specific domain according to the study design (cohort, case-control and cross-sectional). We used an adapted scale for cross-sectional studies, which included the description of statistical tests and appropriateness, sample size, the representativeness of the sample, non-respondents, ascertainment of the exposure, comparability and assessment of the outcome. Primary research studies that were reported more than once were assessed independently due to the different analysis design, outcomes or biomarkers and time assessment used.

## Results

### Study Selection and Description of Studies

The search through 10 electronic databases yielded 3,329 records, of which 2,946 were screened by title and abstract after excluding duplicates (Figure 1). From this primary screening, a total of 124 potential studies were selected for full-text evaluation, of which 38 met the eligibility criteria for this review (a list of excluded studies and reasons for exclusion is available in Supplementary Table 2) (Abou-Saleh et al., 1999; Accortt et al., 2016; Albacar et al., 2011; Armony-Sivan et al., 2012; Blunden et al., 2012; Bodnar et al., 2012; Brandenburg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2014; Fu et al., 2015; Grussu et al., 2007; Gur et al., 2014; Hamazaki et al., 2016; Handley et al., 1977, 1980; Huang et al., 2014; Maes et al., 1992, 2001; Markhus et al., 2013; Mattes et al., 2009; Otto et al., 2003; Parker et al., 2015; Pinto et al., 2016; Ploeckinger et al., 1996; Rees et al., 2009; Robinson et al., 2014; Roomruangwong et al., 2016; Sallis et al., 2014; Shiraishi et al., 2015; Stein et al., 1976; Teofilo et al., 2014; Troisi et al., 2002; Vaz et al., 2014; van Dam et al., 1999; Verly-Miguel et al., 2015; Watanabe et al., 2011). Chong et al. (Chong et al., 2015, 2014); Cassidy-Bushrow et al. (Cassidy-Bushrow et al., 2012), Accortt et al. (Accortt et al., 2016); Pinto et al. (Pinto et al., 2016), Vaz et al. (Vaz et al., 2014), Verly-Miguel et al.

(Verly-Miguel et al., 2015) and Teofilo et al. (Teofilo et al., 2014) reported the same primary research, but investigated different associations between biomarkers and psychological distress. These studies were also included.

Table 2 and Table 3 summarize the characteristics and findings of the studies included in this review. We then grouped the studies, first according to the principal type of nutritional biomarkers, such as micronutrients (vitamins and folate) and amino acids, and second according to the time of assessment and type of outcomes (depression, anxiety and stress). There were 27 cohort (Accortt et al., 2016; Albacar et al., 2011; Armony-Sivan et al., 2012; Blunden et al., 2012; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2014; Fu et al., 2015; Gur et al., 2014; Handley et al., 1980, 1977; Maes et al., 2001; Markhus et al., 2013; Otto et al., 2003; Parker et al., 2015; Pinto et al., 2016; Ploeckinger et al., 1996; Robinson et al., 2014; Roomruangwong et al., 2016; Sallis et al., 2014; Stein et al., 1976; Teofilo et al., 2014; Troisi et al., 2002; van Dam et al., 1999; Wójcik et al., 2006), nine cross-sectional (Abou-Saleh et al., 1999; Grussu et al., 2007; Huang et al., 2014; Maes et al., 1992; Mattes et al., 2009; Shiraishi et al., 2015; Vaz et al., 2014; Verly-Miguel et al., 2015; Watanabe et al., 2010), and 2 case-control (Hamazaki et al., 2016; Rees et al., 2009) (one nested) studies from the regions of America, Asia, Europe and Oceania. The sample sizes varied across the studies, from 18 women in Handley et al. and Stein et al. to 4,101 women in the Brandenbarg et al. study (Brandenbarg et al., 2012; Handley et al., 1977; Stein et al., 1976). The length of follow-up in the cohort studies varied from throughout pregnancy to the 12<sup>th</sup> postnatal month.

The nutritional biomarkers were grouped into the following categories: fatty acids, cholesterol, micronutrients and amino acids. There were 13 studies for fatty acids (Bodnar et al., 2012; Chong et al., 2015; Hamazaki et al., 2016; Markhus et al., 2013; Mattes et al., 2009; Otto et al., 2003; Parker et al., 2015; Pinto et al., 2016; Rees et al., 2009; Sallis et al.,

2014; Shiraishi et al., 2015; Vaz et al., 2014; Verly-Miguel et al., 2015). These studies reported data on polyunsaturated (PUFA), monounsaturated (MUFA), saturated (SFA) and highly unsaturated (HUFA) fatty acids. Fatty acids were measured in red blood cells, plasma and serum. Twelve studies were performed during pregnancy, while only one was conducted in the postnatal period (Otto et al., 2003). Five studies evaluated cholesterol and HDL cholesterol in serum, and of those studies, two studies measured levels during both pregnancy and the postnatal period (Grussu et al., 2007; Ploekinger et al., 1996; Teofilo et al., 2014; Troisi et al., 2002; van Dam et al., 1999).

A total of 21 studies examined micronutrients and amino acids (Abou-Saleh et al., 1999; Accortt et al., 2016; Albacar et al., 2011; Armony-Sivan et al., 2012; Blunden et al., 2012; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2014; Fu et al., 2015; Gur et al., 2014; Handley et al., 1980, 1977; Huang et al., 2014; Maes et al., 2001, 1992; Robinson et al., 2014; Roomruangwong et al., 2016; Stein et al., 1976; Watanabe et al., 2010; Wójcik et al., 2006), of which eight examined vitamin D (Accortt et al., 2016; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Fu et al., 2015; Gur et al., 2014; Huang et al., 2014; Robinson et al., 2014), two vitamin B<sub>12</sub> (Abou-Saleh et al., 1999; Chong et al., 2014), four folate (Blunden et al., 2012; Bodnar et al., 2012; Chong et al., 2014; Watanabe et al., 2010), two zinc (Roomruangwong et al., 2016; Wójcik et al., 2006), two ferritin (Albacar et al., 2011; Armony-Sivan et al., 2012), and eight amino acids (Abou-Saleh et al., 1999; Bodnar et al., 2012; Handley et al., 1980, 1977, Maes et al., 2001, 1992; Stein et al., 1976; Watanabe et al., 2010). Vitamin D was measured in serum in all of the studies, and only one study assessed levels of vitamin D in the postnatal period (Fu et al., 2015).

Bodnar et al. (Bodnar et al., 2012) studied several biomarkers simultaneously by estimating factor scores for fatty acids, micronutrients and carotenoids through principal components analysis.

Depression was investigated in 35 studies (Abou-Saleh et al., 1999; Accortt et al., 2016; Albacar et al., 2011; Armony-Sivan et al., 2012; Blunden et al., 2012; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2015; Fu et al., 2015; Grussu et al., 2007; Gur et al., 2014; Handley et al., 1980, 1977; Huang et al., 2014; Maes et al., 1992; Markhus et al., 2013; Mattes et al., 2009; Otto et al., 2003; Parker et al., 2015; Pinto et al., 2016; Ploekinger et al., 1996; Rees et al., 2009; Robinson et al., 2014; Roomruangwong et al., 2016; Sallis et al., 2014; Shiraishi et al., 2015; Stein et al., 1976; Teofilo et al., 2014; Troisi et al., 2002; van Dam et al., 1999; Vaz et al., 2014; Watanabe et al., 2010; Wójcik et al., 2006), anxiety in seven (Chong et al., 2015; Huang et al., 2014; Maes et al., 2001, 1992; Roomruangwong et al., 2016; Troisi et al., 2002; Verly-Miguel et al., 2015), stress in one (Huang et al., 2014), and psychological distress as a composite assessment in a single study (Hamazaki et al., 2016).

There were five studies that assessed depression and anxiety at the same time in pregnancy and postpartum (Chong et al., 2015; Huang et al., 2014; Maes et al., 1992; Roomruangwong et al., 2016; Troisi et al., 2002). However, those studies did not report data on the associations of comorbidity. Two other studies reported data on the associations between nutritional biomarkers and depression through an analysis adjusted by anxiety (Roomruangwong et al., 2016; Teofilo et al., 2014).

Depression frequencies varied from 5.8% to 61.6%, depending on the assessment tool, the cut-off point of the scale used, the assessment period and population. The Edinburgh Postnatal Depression Scale (EPDS) was the most commonly used scale for assessing depression (in 19 of 35 studies), but each study used different cut-off points (range: 8 to 15)

and applied the scale to both antenatal and postnatal assessment. The Spielberger's State-Trait Anxiety Index (STAI) was the most commonly used scale to assess anxiety in both antenatal and postnatal periods (in 5 of 7 studies) (Chong et al., 2015; Maes et al., 2001, 1992; Roomruangwong et al., 2016; Troisi et al., 2002). Stress was assessed through the Depression, Anxiety and Stress Scales 21-item short form (DASS-21) (Huang et al., 2014). The data were reported separately for each of the subscales (Huang et al., 2014). The assessment of psychological distress, as a whole was evaluated by the Kessler Psychological Distress Scale (Hamazaki et al., 2016).

### Methodological Quality

The studies' NOS scores are presented in Table 2 and the summary by item of each domain of the NOS is shown in Figure 2. We found only two out of 38 studies of low quality (NOS scores < 4), and those studies referred to tryptophan and cholesterol (Ploeckinger et al., 1996; Stein et al., 1976). For fatty acids, 77% (10 from 13) were studies of high quality (Bodnar et al., 2012; Chong et al., 2015; Hamazaki et al., 2016; Markhus et al., 2013; Mattes et al., 2009; Parker et al., 2015; Pinto et al., 2016; Rees et al., 2009; Vaz et al., 2014; Verly-Miguel et al., 2015) (NOS scores  $\geq 7$ ). For cholesterol, there were two studies of high quality (Teofilo et al., 2014; van Dam et al., 1999) and two of moderate quality (Grussu et al., 2007; Troisi et al., 2002). Most studies of vitamin D were of high quality (7 of 8 studies) (Accortt et al., 2016; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Fu et al., 2015; Huang et al., 2014; Robinson et al., 2014). The majority of studies of vitamin B<sub>12</sub> and folate were of moderate quality (3 of 5 studies) (Abou-Saleh et al., 1999; Blunden et al., 2012; Bodnar et al., 2012; Chong et al., 2014; Watanabe et al., 2010).

Studies of ferritin and zinc were all of moderate quality (Albacar et al., 2011; Armony-Sivan et al., 2012; Roomruangwong et al., 2016; Wójcik et al., 2006).

Four cohort studies reported the exclusion of women with the outcomes at the start of the study when the quality of studies was analyzed according to each domain item (Chong et al., 2015, 2014; Gur et al., 2014; van Dam et al., 1999). Twelve cohort studies adjusted for confounding factors in the design and/or data analysis (Accortt et al., 2016; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2014; Fu et al., 2015; Otto et al., 2003; Robinson et al., 2014; Sallis et al., 2014; Teofilo et al., 2014; van Dam et al., 1999). No cross-sectional study provided information on the sample size and comparability between respondents and non-respondents (Abou-Saleh et al., 1999; Grussu et al., 2007; Huang et al., 2014; Maes et al., 1992; Mattes et al., 2009; Shiraishi et al., 2015; Vaz et al., 2014; Verly-Miguel et al., 2015; Watanabe et al., 2010). Case-control studies provided adequate information for most of the items (Hamazaki et al., 2016; Rees et al., 2009).

## **Main Findings**

The included studies reported findings obtained with a variety of different measures of association and over a time span from pregnancy to the postnatal period (Tables 2 and 3). A summary of the associations between biomarkers and depression in women during pregnancy and the first postpartum year reported in at least two included studies is shown in Table 4.

## **FATTY ACIDS**

Associations between fatty acids and depression were evaluated in total of 11 studies, those between fatty acids and anxiety were evaluated in two studies, and those between fatty acids and psychological distress were evaluated in one study.

### ***Depression in Pregnancy***

There were seven studies reporting data on fatty acids and their relation to depression in pregnancy.

Three studies found that  $\omega$ -3 PUFA levels were not significantly associated with depression during pregnancy (Chong et al., 2015; Mattes et al., 2009; Rees et al., 2009). A longitudinal analysis showed that higher serum  $\omega$ -3 PUFA levels were associated with a lower probability of developing depression during pregnancy ( $n = 172$ , OR = 0.98, 95% CI = 0.96 - 0.99) (Pinto et al., 2016).

Total  $\omega$ -6 PUFAs were found to be a risk factor for depression during pregnancy, but this association was not statistically significant (Chong et al., 2015; Mattes et al., 2009; Pinto et al., 2016; Rees et al., 2009). One study examined the associations between serum levels of total  $\omega$ -3,  $\omega$ -6 HUFA and total MUFA and major depressive episodes in the first trimester, finding a non-significant association between them ( $n = 194$ ) (Vaz et al., 2014).

There were conflicting results for the associations of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and fatty acid ratios (such as  $\omega$ -6/ $\omega$ -3) with depression across the studies, even if an adjusted analysis was applied (Chong et al., 2015; Markhus et al., 2013; Mattes et al., 2009; Otto et al., 2003; Parker et al., 2015; Pinto et al., 2016; Rees et al., 2009).

### ***Depression in Postpartum***

There were three studies assessing fatty acids and depression in postpartum.

Parker et al. (Parker et al., 2015) found that lower levels of red blood cell total  $\omega$ -3 and higher levels of red blood cell  $\omega$ -6 PUFA were associated with a higher probability of depression (EPDS  $\geq 10$ ) ( $n = 895$ , adjusted ORs = 1.1,  $p < 0.05$  for both).

Levels of red blood cell total SFA and total MUFAs were inversely and non-significantly correlated with EPDS scores in the third postnatal month (Markhus et al., 2013; Parker et al., 2015).

The postnatal change between the periods after delivery and the 32<sup>nd</sup> postnatal week in plasma DHA/ $\omega$ -6 DPA ratio showed that a 1-unit increase produced a decrease in the



probability of depression (EPDS  $\geq 10$ ) ( $n = 112$ , adjusted OR = 0.88,  $p = 0.03$ ) (Otto et al., 2003).

### ***Anxiety and Psychological Distress***

Serum DHA levels were significantly associated with anxiety in the first trimester ( $n = 228$ , adjusted ORs = 1.95, 95% CI = 1.00 - 3.77,  $p = 0.047$ ), but serum  $\omega$ -6 and  $\omega$ -3 PUFA levels were not significantly associated with anxiety (Verly-Miguel et al., 2015). In the third trimester, there were significant positive associations between plasma  $\omega$ -6/  $\omega$ -3, AA/DHA, and AA/EPA levels and anxiety; additionally, there were negative associations between total  $\omega$ -3 PUFA levels and anxiety ( $n = 698$ ) (Chong et al., 2015). None of these plasma fatty acids were shown to be significantly associated with anxiety three months postpartum ( $p < 0.05$ ) (Chong et al., 2015).

High serum EPA levels were associated with a low risk of having psychological distress (Kessler scale scores  $\geq 9$ ) in early pregnancy ( $n = 283$ , adjusted OR = 0.47, 95% CI = 0.30 - 0.73) (Hamazaki et al., 2016).

## **CHOLESTEROL**

A total of 5 studies evaluated the association between cholesterol and depression (HDL-cholesterol in two of them) (Grussu et al., 2007; Ploekinger et al., 1996; Teofilo et al., 2014; Troisi et al., 2002; van Dam et al., 1999), and one examined the association between cholesterol and anxiety (Troisi et al., 2002).

### ***Depression in Pregnancy***

There were two studies assessing depression in pregnancy and HDL-cholesterol levels (Teofilo et al., 2014; Troisi et al., 2002) and one study examining depression and total cholesterol (Troisi et al., 2002). One out of two studies reported a significant inverse association between a 1-unit increase of HDL-cholesterol and longitudinal EPDS score

changes during pregnancy ( $n = 238$ ) (Teofilo et al., 2014), while the other study did not ( $n = 47$ ) (Troisi et al., 2002).

### ***Depression in Postpartum***

There were four studies reporting data on depression and cholesterol in postpartum (Grussu et al., 2007; Ploekinger et al., 1996; Troisi et al., 2002; van Dam et al., 1999). Three studies assessed the association between depression and cholesterol changes from pregnancy to postpartum (Ploekinger et al., 1996; Troisi et al., 2002; van Dam et al., 1999). One out of three studies found a significant inverse correlation between depression, as measured by Zung scores, and cholesterol changes, with an exception for the 4<sup>th</sup> day of assessment ( $n = 20$ ). The other two studies did not report significant associations (sample sizes varied from 47 to 405) (Troisi et al., 2002; van Dam et al., 1999).

Two studies showed a significant inverse association between depression and cholesterol in early postpartum (Grussu et al., 2007; Troisi et al., 2002).

### ***Anxiety***

Cholesterol was found to be inversely but non-significantly correlated with STAI scores in the antenatal and postpartum periods, while serum HDL-cholesterol was significantly associated with anxiety in the postnatal period ( $n = 47$ ,  $r = -0.34$ ,  $p = 0.02$ ) (Troisi et al., 2002).

## **MICRONUTRIENTS and AMINO ACIDS**

Micronutrients and amino acids were investigated in 20 studies investigating depression (Abou-Saleh et al., 1999; Accortt et al., 2016; Albacar et al., 2011; Armony-Sivan et al., 2012; Blunden et al., 2012; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2014; Fu et al., 2015; Gur et al., 2014; Handley et al., 1980, 1977; Huang et al., 2014; Maes et al., 1992; Robinson et al., 2014; Roomruangwong et al., 2016;

Stein et al., 1976; Watanabe et al., 2010; Wójcik et al., 2006), and three studies in relation to anxiety (Huang et al., 2014; Maes et al., 2001, 1992; Roomruangwong et al., 2016).

## **Vitamin D**

There were eight studies examining the relationship between vitamin D and depression (Accortt et al., 2016; Bodnar et al., 2012; Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Fu et al., 2015; Gur et al., 2014; Huang et al., 2014; Robinson et al., 2014). One of these studies also examined anxiety and stress (Huang et al., 2014).

### ***Depression in Pregnancy***

A total of three studies reported on vitamin D and depression in pregnancy (Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Huang et al., 2014), of which two found significant associations (Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012). Brandenbarg et al. (Brandenbarg et al., 2012) found that serum vitamin D deficiency ( $\leq 29.9$  nM) and insufficiency (30-49.9 nM) were significantly associated with an increased likelihood of depression, as indicated by scores of  $\geq 16$  on the Center for Epidemiological Studies Depression Scale (CESD) during pregnancy in the adjusted analysis (major cohort between the included studies,  $n = 4,101$ ) (adjusted ORs (95% CI): 1.48 (1.13 - 1.95) and 1.44 (1.12 - 1.85) for vitamin D deficiency and insufficiency, respectively) (Huang et al., 2014). The other study found that a 1-unit increase of log serum vitamin D levels was significantly associated with a 46% decreased likelihood of depression (CESD  $\geq 16$ ) ( $n = 178$ ,  $p = 0.046$ ) in the adjusted analysis (Cassidy-Bushrow et al., 2012).

### ***Depression in Postpartum***

A total of four studies evaluated depression and vitamin D in postpartum (Accortt et al., 2016; Fu et al., 2015; Gur et al., 2014; Robinson et al., 2014). Three of the four studies (75%) showed a significant inverse association between serum vitamin D levels and depression

scores, which were evaluated by the EDPS in the early and/or late postnatal time frame (sample sizes varying from 208 to 929) (Fu et al., 2015; Gur et al., 2014; Robinson et al., 2014). The remaining study did not show this association (Accortt et al., 2016) ( $n = 91$ ). However, Accortt et al. (Accortt et al., 2016) showed that higher levels of pro-inflammatory cytokines, such as interleukin-6 and the interleukin-6/interleukin-10 ratio, significantly moderate the association between lower prenatal vitamin D levels and higher postpartum depression symptoms.

### ***Anxiety and Stress***

Only one out of eight (12.5%) studies of vitamin D investigated the association with anxiety and stress in pregnancy (Huang et al., 2014). Huang et al. (Huang et al., 2014) investigated anxiety and stress by using the Depression, Anxiety and Stress Scales (DASS) in a cross-sectional study of pregnant women, and the results showed a non-significant positive association between serum vitamin D levels and both scales scores ( $n = 498$ , adjusted linear coefficients: 0.019 ( $p = 0.398$ ) and 0.037 ( $p = 0.281$ ), respectively).

### **Vitamin B<sub>12</sub> and Folate**

There were three studies on the association between depression and folate (Blunden et al., 2012; Chong et al., 2014; Watanabe et al., 2010) and two studies on the association between depression and vitamin B<sub>12</sub> (Abou-Saleh et al., 1999; Chong et al., 2014). There is no study assessing the association between anxiety and vitamin B<sub>12</sub> and folate. Three studies reported that pregnant women used folate and vitamin B<sub>12</sub> supplements (Blunden et al., 2012; Chong et al., 2014; Watanabe et al., 2011).

### ***Depression in Pregnancy***

Only one study evaluated vitamin B<sub>12</sub> levels and depression during the prenatal period and found a non-significant association between them ( $n = 967$ , adjusted OR = 1.07, 95% CI =

0.79 - 1.45,  $p = 0.672$ ) (Chong et al., 2014). One study of folate reported a significant association with depression, as measured by the EPDS, in the 26<sup>th</sup>-28<sup>th</sup> gestational week ( $n = 967$ , adjusted OR = 0.69, 95% CI = 0.52 - 0.94) (Chong et al., 2014), while the another study (50%) did not. In this later study, depression was evaluated by the CESD in the 6<sup>th</sup>-11<sup>th</sup> gestational week ( $n = 86$ ) (Watanabe et al., 2010).

### ***Depression in Postpartum***

There were two studies evaluating the association between depression and vitamin B<sub>12</sub> (Abou-Saleh et al., 1999; Chong et al., 2014) and two studies evaluating the association between depression and folate (Blunden et al., 2012; Chong et al., 2014) in postpartum.

For vitamin B<sub>12</sub>, one study (50%) found a significant positive correlation with EPDS scores ( $n = 62$ ) (Abou-Saleh et al., 1999). Meanwhile, the other study (50%) reported no significant association ( $n = 967$ , adjusted OR = 1.08, 95% CI = 0.83 - 1.40) (Chong et al., 2014).

One out of two studies of folate (50%) identified a significant association with depression evaluated in the third postpartum month ( $n = 967$ ) (Chong et al., 2014), while the other study, which assessed depression in the 6<sup>th</sup>-12<sup>th</sup> postpartum month ( $n = 2,856$ ), did not find a significant association (Blunden et al., 2012).

### **Amino Acids**

A total of seven studies reported data on the association between amino acids and depression (Abou-Saleh et al., 1999; Handley et al., 1980, 1977; Maes et al., 1992; Stein et al., 1976; Watanabe et al., 2010), and two studies investigated the association between amino acids and anxiety (Maes et al., 2001, 1992).

### ***Depression in Pregnancy***

Only one study assessed homocysteine and depression in pregnancy and found no association between them ( $n = 86$ , adjusted OR = 0.63, 95% CI = 0.23-1.72) (Watanabe et al., 2010).

***Depression in Postpartum***

There were a total of five studies assessing the relation between the amino acids and depression (Abou-Saleh et al., 1999; Handley et al., 1980, 1977; Maes et al., 1992; Stein et al., 1976). Three studies (75%) found a significant inverse correlation between tryptophan and depression (sample sizes varied from 18 to 62) (Abou-Saleh et al., 1999; Handley et al., 1977; Stein et al., 1976), and one study (25%) did not ( $n = 71$ ) (Handley et al., 1980).

Furthermore, one study evaluated the ratio of plasma tryptophan and the sum of the levels of valine, leucine, isoleucine and phenylalanine and found a significant inverse correlation with depression ( $n = 29$ ,  $r = -0.46$ ,  $p = 0.007$ ), as measured by Zung scores (Maes et al., 1992).

***Anxiety***

The ratio of plasma tryptophan and the sum of the levels of valine, leucine, isoleucine and phenylalanine was significantly inversely correlated with anxiety, as measured by Zung scores and STAI scores ( $n = 29$ ) (Maes et al., 1992). Another study reported that changes in plasma phenylalanine were significantly correlated with changes in STAI scores from the 3<sup>rd</sup>-6<sup>th</sup> day before delivery to the 1<sup>st</sup> and 3<sup>rd</sup> postnatal day ( $n = 98$ ,  $r = 0.16$ ,  $p = 0.04$ ) (Maes et al., 2001).

***Ferritin***

A total of two studies reported data on the association between ferritin and depression (Albacar et al., 2011; Armony-Sivan et al., 2012), and no study assessed the relationship between ferritin and anxiety.

***Depression in Postpartum***

One study reported a significant association between lower levels of serum ferritin ( $< 7.26$   $\mu\text{g/L}$ ) and a higher risk of depression (scored by the EPDS as  $> 9$ ) at 8-32 weeks postnatally

( $n = 729$ , OR = 3.73; 95% CI = 1.84-7.56) (Albacar et al., 2011), while the other study did not find this association ( $n = 567$ ) (Armony-Sivan et al., 2012).

## **Zinc**

A total of two studies investigated the relation between zinc and depression (Roomruangwong et al., 2016; Wójcik et al., 2006), and one study examined the association between zinc and anxiety (Roomruangwong et al., 2016).

### ***Depression in Pregnancy and Postpartum***

One out of two studies reported an OR (95% CI) of 4.16 (1.42 - 12.22) of having depression, scored as  $\geq 11$  on the EPDS, in the third trimester with a 1-unit increase of the inverse of serum zinc levels (Roomruangwong et al., 2016).

Two studies (Roomruangwong et al., 2016; Wójcik et al., 2006) found that serum zinc levels were significantly inversely correlated with depression symptoms. One of these studies assessed depression in the third trimester and in the 4<sup>th</sup>-6<sup>th</sup> postpartum week (Roomruangwong et al., 2016), and the other study assessed depression in the 3<sup>rd</sup> and 30<sup>th</sup> postpartum day (Wójcik et al., 2006) (sample sizes of studies less than 75).

## **Anxiety**

Roomruangwong et al. (Roomruangwong et al., 2016) found a non-significant inverse correlation between zinc levels and STAI scores in the third trimester and in the 4<sup>th</sup>-6<sup>th</sup> postpartum week ( $n = 72$ ,  $r = -0.042$ ,  $p = 0.729$ ).

## **PATTERNS of FATTY ACIDS, CAROTENOIDS and MICRONUTRIENTS**

Bodnar et al. (Bodnar et al., 2012) found that the highest tertiles of essential fatty acids and carotenoid scores were associated with a decreased risk of major depressive disorder during pregnancy. The highest tertile of micronutrient scores showed a decrease in the risk of a

major depressive disorder. All of the associations were non-significant after adjusting for several confounders.

## Discussion

The current review summarizes the evidence of associations between a broad number of nutritional biomarkers and psychological distress. The variability across the studies with respect to timing of psychological assessments, the scales employed for diagnosis/screening and the measures of association did not allow for a formal pooled analysis. Furthermore, our review found conflicting results for most of the relationships studied. Fatty acids were the most frequently studied biomarker, but studies showed divergent or non-significant associations. Most studies assessing serum vitamin D presented a significant inverse association with depression during pregnancy and in the postnatal period. The same trend was observed between plasma tryptophan levels and postnatal depression. Anxiety and stress were under-investigated in relation to nutritional biomarkers.

Studies identified psychological distress using clinical and self-reported interviews. Several different tools were used to assess depression, and even if studies applied the same scale, the diagnostic/screening cut-off point or the assessment time point for each biomarker varied between the studies. Additionally, for the comparison of results between the studies, it is important to consider that depression cases could have been mild to moderate and in a heterogeneous clinical population (based on the inclusion/exclusion criteria and sample characteristics for each study). Furthermore, studies assessing depression less than one week after delivery could be confounded by the “baby blues” or postpartum blues, even if depression was evaluated as a continuous score. Therefore, all these issues, together with the biomarkers limitations, could have attenuated or weakened the power to find associations or comparisons across the studies.



Associations between nutritional biomarkers and depression/anxiety could have been due to chance as a result of the small study sample sizes. Studies with small sample size are underpowered to detect significant associations. In our review, 14 out of 38 (37%) studies presented sample sizes smaller than 100 women (Abou-Saleh et al., 1999; Accortt et al., 2016; Handley et al., 1977, 1980, Maes et al., 1992, 2001; Markhus et al., 2013; Ploeckinger et al., 1996; Rees et al., 2009; Roomruangwong et al., 2016; Stein et al., 1976; Troisi et al., 2002; Watanabe et al., 2010; Wójcik et al., 2006). As a consequence of the small sample sizes, their findings need to be considered with caution. However, when the sample size is larger, there is the possibility of finding a significant association, especially when the association is small, because the sample better represents the population from which it is derived.

Furthermore, a total of 15 studies assessing correlations did not perform an adjusted analysis for potential confounders. Studies with adjusted analyses used at least one of the maternal confounders, such as age/parity/marital status, or a comprehensive list.

We did not find any study that assessed the comorbidity of depression and anxiety during pregnancy and postpartum and its association with nutritional biomarkers. However, there were studies evaluating both of them separately or in the adjusted analysis. The presence of comorbidity in the studies, which was not assessed, could have overestimated the strength of association (being positive or negative) between each outcome and a certain nutritional biomarker.

Some studies reported the use of supplementation independently when the biomarker was measured. This fact could potentiate or interfere with the development of depression (Accortt et al., 2016; Blunden et al., 2012; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2014; Gur et al., 2014; Markhus et al., 2013), especially in postnatal depression, for which there

was insufficient evidence addressing dietary supplementation (selenium, DHA or EPA or other supplement) as a preventative measure (Miller et al., 2013).

Essential and non-essential fatty acids were investigated in relation to psychological distress. They were measured in different blood fractions. It is of note that erythrocytes reflect the long term intake of  $\omega$ -3 PUFA and trans fatty acids among the other fractions, with less biological variability for EPA and DHA and a half-life of 120 days, and is superior to plasma lipoproteins (Harris and Thomas, 2010; Sun et al., 2007). Therefore, studies that measured fatty acids in erythrocytes showed relationships with depression characterized by less variability and sensitivity to recent intake than studies using other fractions (Bodnar et al., 2012; Markhus et al., 2013; Mattes et al., 2009; Parker et al., 2015; Sallis et al., 2014).

Additionally, it is important to note that studies reported fatty acids as absolute amounts (Chong et al., 2015; Pinto et al., 2016; Shiraishi et al., 2015; Verly-Miguel et al., 2015), or percentages of total fatty acids (Bodnar et al., 2012; Hamazaki et al., 2016; Markhus et al., 2013; Mattes et al., 2009; Otto et al., 2003; Parker et al., 2015; Rees et al., 2009; Sallis et al., 2014; Vaz et al., 2014). These two reporting approaches of fatty acids can lead to different association results across studies, because when fatty acids are expressed as a weight percentage, each one is affected by changes in the other measured fatty acids. In the case of absolute amount, the results are independent for each fatty acid measured (Mocking et al., 2012; Schwertner and Mosser, 1993; Sergeant et al., 2016).

It is worth noting that the lack of evidence of a robust association between red blood cell DHA and EPA and perinatal-onset, prenatal and postnatal depression is based on an approach free of confounding and reverse causality (Sallis et al., 2014). There are problems in some observational studies included in our systematic review. Therefore, the associations found in those studies may not be actual associations. More studies in different settings free of confounding and reverse causality are necessary to confirm this finding.

The findings of Teofilo et al. (Teofilo et al., 2014) regarding depression and serum HDL cholesterol should be considered with caution, as the authors have included a subsample of women with supplementation of 1.08 g EPA + 0.72 g DHA per day. However, there is evidence showing that DHA and EPA supplementation does not have a beneficial effect on perinatal depression symptoms (Jans et al., 2010). It is important to consider the possible effect of DHA+EPA supplementation on HDL-cholesterol levels (Jacobson et al., 2012; Wei and Jacobson, 2011), and in this case, on our diverse results for the associations with DHA and EPA, which could have introduced bias into the findings.

Evidence from adult women showed a positive relationship between high HDL cholesterol levels and higher depression scores, the standardized mean difference being 0.20 (95% CI 0.07 - 0.34;  $p < 0.01$ ;  $Q = 2.10$ ; pooled data from four studies). For total cholesterol, the relationship was inverse, with a standardized mean difference of -0.23 (95% CI -0.37- -0.10;  $p < 0.01$ ;  $Q = 18.64$ , data pooled from 12 studies) (Shin et al., 2008).

The findings of Accortt et al. (Accortt et al., 2016) should be interpreted with caution because women received vitamin D supplements. Thus, this supplementation could have attenuated the development of postnatal depression from the first trimester to the first postnatal month, despite the fact that the interaction with pro-inflammatory cytokines remained significant. Several factors can influence vitamin D levels, such as the season of vitamin D measurements given different to the exposures to sun-light, ethnicity and vitamin D supplementation. However, not all of the studies reported data on these factors or the percentages of women with deficient or insufficient levels. A recent review investigated vitamin D levels measured during pregnancy and their association with postpartum depression, the results of which suggested a correlation (Mahmood et al., 2015). Three studies were included, one of which classified depression by antidepressant use (Nielsen et al., 2013). However, the use of antidepressants was an exclusion criterion in our review.

In addition, the effect of vitamin D on depression was investigated through a systematic review with meta-analysis in the adult population. For cohort studies, there was a significant increase in the hazard ratio of depression for the lowest versus the highest serum vitamin D categories (vitamin D deficiency and normal levels defined by each study) (pooled HR = 2.21, 95% CI = 1.40 - 3.49,  $p < 0.001$ ,  $I^2 = 21\%$ ,  $n = 3$  studies and 8,815 participants). In the case of cross-sectional studies, the pooled OR was 1.31 (95% CI = 1.0 - 1.75,  $p = 0.05$ ,  $I^2 = 54\%$ ,  $n = 9$  studies and 22,318 participants) for depression for the lowest versus the highest vitamin D categories (Anglin et al., 2013). Nevertheless, it is well known that women are under different physiological, social, physical and emotional situations during pregnancy and postpartum.

Folate and iron are recommended as daily supplements as early as possible in pregnancy because they reduce the risk of negative maternal and neonatal outcomes (WHO, 2012). However, for antenatal/postnatal depression, there is still inconsistent evidence in our review to support an association with folate levels.

Some studies selected samples based on ethnicity criteria (Accortt et al., 2016; Albacar et al., 2011; Cassidy-Bushrow et al., 2012; Chong et al., 2015, 2014; Fu et al., 2015; Robinson et al., 2014; Sallis et al., 2014; van Dam et al., 1999), while other studies performed analyses adjusted by ethnicity (Brandenbarg et al., 2012; Chong et al., 2015, 2014; Huang et al., 2014), or only reported these data (Bodnar et al., 2012; Vaz et al., 2014). However, the studied samples are from numerous countries (in America, Asia, Europe and Oceania), which indicated some important general characteristics, such as sun-light exposure, dietary habits, and income status of the country (which is also associated with the depression/anxiety prevalence rate, as previously mentioned). For the studies with samples restricted to specific ethnicities, the results should be considered with caution, as they are not generalizable to the overall population.

Maternal nutritional biomarkers are the biological results of dietary intake through different metabolic/biochemical processes. At the same time, these biomarkers play roles in metabolic pathways; some of them link to neural processes. The possible biological plausibility of biomarkers on depression are as follows: a) vitamin D acts in neurotransmitter synthesis and calcium homeostasis (Garcion et al., 2002; McCann and Ames, 2008); b) vitamin B<sub>12</sub> is linked to the efficient functioning of the folate cycle, which is necessary for the synthesis and regeneration of tetrahydrobiopterin, an essential cofactor for the conversion of amino acids to neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, adrenaline) (Bottiglieri, 2005; Kennedy, 2016); c) tryptophan acts in the synthesis of serotonin, melatonin and kinurenines (Fernstrom, 2013); and d) fatty acids and cholesterol affect membrane structures, neurotransmitter uptake and signal transmission (Bodnar and Wisner, 2005; Scanlon et al., 2001).

The bioavailability of these nutritional biomarkers in the body is mostly dependent upon the quality of dietary intake, which could be influenced by psychosocial factors during pregnancy and during the postpartum period (George et al., 2005; Fowles et al., 2011; Hurley et al., 2005). In pregnant women, psychosocial distress is related to worse dietary quality (Fowles et al., 2011). Therefore, psychosocial factors should also be considered in women during pregnancy and the postpartum period when attending routine care to avoid potential adverse outcomes.

### **Strengths, Limitations and Future Directions**

Our study has several strengths, such as the broad number of nutritional biomarkers examined; the extensive literature search of terms and the number of databases included; and the hand-searching, and forward citation tracking and assessment of studies' methodological quality. However, we cannot reject the possibility of publication bias.

Some limitations of our current review need to be highlighted. First, we cannot combine the data from the studies due to the higher variability of association measures given as correlations, odds ratios, longitudinal or linear or logistic regression coefficients, relative risk and their 95% confidence intervals or *p*-values. Studies that assessed the same biomarkers or anxiety or stress and the outcomes and/or exposure expressed as continuous or categorical variables were few in number. Another limitation was only including studies that provided data on association measures. Studies that did not report the magnitude of associations were not included in our review.

Finally, we note some possible future directions that emerged from this systematic review (Table 5). Briefly, there is a lack of data on nutritional biomarkers and anxiety and psychological stress. Additional well-designed epidemiological studies are needed, as well as reports of the ethnicity of studied sample and other important confounders. Depression during pregnancy and postpartum should be assessed by a single standard tool through the studies, i.e., the EPDS or a diagnostic interview. Fatty acid levels should be presented in absolute concentrations. Nutritional supplementation, women's nutritional status, trace elements, amino acids, vitamins, lipids and psychological distress should be assessed throughout both pregnancy and postpartum in prospective studies.

## Conclusions

This systematic review summarized the current evidence of a broad number of nutritional biomarkers and depression/anxiety during pregnancy and postpartum. Pregnant women with lower vitamin D levels had an increased probability of depression during pregnancy and in the postnatal period. To reinforce this finding, Vaziri et al. (2016) reported that consuming 2000 IU of vitamin D daily from the 26<sup>th</sup>-28<sup>th</sup> gestational week until childbirth significantly reduced the EPDS scores assessed in the 38<sup>th</sup>-40<sup>th</sup> gestational week and the fourth and eighth

week after birth ( $n = 169$ , randomized clinical trial,  $p < 0.001$ , women with scores of EPDS  $>13$  were excluded) (Vaziri et al., 2016). There are a small number of studies evaluating anxiety and stress in comparison to depression. For fatty acids, studies were so diverse that we suggest that new evidence providing levels of nutritional biomarkers as absolute concentrations and reporting measures of the risk of adverse outcomes more consistently are needed. Micronutrients were under investigated; therefore, additional longitudinal studies are necessary, particularly those examining vitamin A and minerals involved in neurotransmitter function. Women's nutritional status should be reported in studies of micronutrients. In summary, further evidence is necessary for guiding clinical practice in the relationships of nutritional biomarkers and depression/anxiety during pregnancy and postpartum.

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### **Contributors**

JT, MCV, DP, LP and GK designed the study and wrote the protocol. JT and JL managed the literature searches and data extraction. JT and FR conducted the quality assessment. MCV

assisted with the literature searches, data extraction and quality assessment. JT performed the analysis and wrote the manuscript. All authors contributed to the editing and have approved the final manuscript.

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JT, MCV, DP, LP and GK designed the study and wrote the protocol. JT and JL managed the literature searches and data extraction. JT and FR conducted the quality assessment. MCV assisted with the literature searches, data extraction and quality assessment. JT performed the analysis and wrote the manuscript. All authors contributed to the editing and have approved the final manuscript.

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**Figure 1.** Flowchart of study selection according to the PRISMA guideline.

**Figure 2.** Methodological quality assessed by the Newcastle-Ottawa scale. Studies were considered as being high methodological quality if they received the maximum number of points for the item in the specific domain and low quality if they did not. Methodological quality is presented as a percentage of number of studies with high, moderate and low quality in each item of the specific domain by epidemiological design. High = high methodological quality, Moderate = moderate methodological quality, Low = low methodological quality. A) Cohort studies; B) cross-sectional studies; C) case-control studies.

**Table 1.** PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Participants	Women during pregnancy and/or at the first year of postpartum period.	
Intervention	Maternal nutritional biomarkers (such as fatty acids, vitamins, minerals and amino acids) measured in blood.	
Comparators	None specified	
Outcomes	Psychological distress (depression, anxiety and psychological stress) diagnosed using symptom questionnaires, screening measures and/or diagnostic assessments.	Outcomes assessed only by medication use (such as antidepressant to diagnose a case of depression without a symptom questionnaire, screening measure and/or diagnostic assessment) or if the patient had other evaluated mental disorders (e.g. bipolar disorder) or

physiological stress (not being a psychological evaluation).

Study design  
Prospective cohort, cross-sectional, case-control designs (nested case-control and case-cohort) and intervention studies (only baseline data).

**Table 2.** Characteristics of included studies evaluating the associations between fatty acids and cholesterol and psychological distress in women during pregnancy and the first postpartum year.

Study, country	Study design, sample size and age (mean $\pm$ SD)	Psychological distress (% assessment tool, timing)	Nutritional biomarker (sample, mean $\pm$ SD or median (IR), timing)	Main results	NOS scores
<b>FATTY ACIDS</b>					
<b>Outcomes in pregnancy</b>					
Pinto et al., 2016, Brazil <sup>1,2</sup>	Cohort, $n = 172$ , NR mean age	33.7% at 5 <sup>th</sup> -13 <sup>th</sup> gw, 18.9% at 20 <sup>th</sup> -26 <sup>th</sup> gw and 17.4% at 30 <sup>th</sup> -36 <sup>th</sup> gw scored $\geq$ 11 in Portuguese version of EPDS.	In serum ( $\mu\text{g/mL}$ ): LA = 705.3 $\pm$ 127.9, AA = 211.0 $\pm$ 50.9, AdA = 9.1 $\pm$ 3.4, ALA = 14.9 $\pm$ 5.3, EPA = 9.9 $\pm$ 5.4, DPA = 12.2 $\pm$ 3.7, DHA = 56.4 $\pm$ 15.9, total $\omega$ -6 PUFA = 993.2 $\pm$ 176.2 and total $\omega$ -3 PUFA = 93.6 $\pm$ 25.4 at 5 <sup>th</sup> -13 <sup>th</sup> . Fatty acids were also measured at 20 <sup>th</sup> -26 <sup>th</sup> and 30 <sup>th</sup> -36 <sup>th</sup> gw.	ORs (95% CI) (within effect, random intercept logistic model, longitudinal data) of depression symptoms during pregnancy and levels of serum fatty acids were: 1.0 (1-1.01) for LA, 1.0 (0.99-1.02) for AA, 0.94 (0.81-1.08) for AdA, 0.97 (0.90-1.04) for ALA, 0.92 (0.86-0.99) for EPA, 0.87 (0.77-0.99) for DPA, 0.96 (0.93-0.99) for DHA, 1.40 (1.09-1.79) for $\omega$ -6/ $\omega$ -3, 1.0 (1.0-1.0) for total $\omega$ -6 PUFA,	7

Hamazaki et al., 2016, Japan	<p>Nested case-control, <b>n = 283:</b> <math>31.5 \pm 5.0</math>; control group = <math>31.5 \pm 4.9</math> yr</p>	<p>Cases scored <math>\geq 9</math> in Japanese version of the Kessler psychological distress scale at first trimester.</p>	<p>In serum (%): for case group EPA = 0.53 (0.41-0.79), DPA = 0.42 (0.33-0.53) and DHA = 3.39 (2.73-4.06); for control group EPA = 0.62 (0.46-0.94), DPA = 0.45 (0.37-0.56) and DHA = 3.56 (2.95-4.09) at 9<sup>th</sup>-14<sup>th</sup> gw and 25% after 15<sup>th</sup> gw</p>	<p>0.98 (0.96-0.99) for total <math>\omega</math>-3 PUFA. All models were adjusted for gestational age, previous history of depression, marital status, inter-partum interval, pre-pregnancy BMI and planned pregnancy.</p> <p>ORs (95% CI) of psychological distress in early pregnancy were for the highest versus lowest serum tertiles: 0.47 (0.30-0.73) for EPA, 0.73 (0.48-1.13) for DPA, 0.79 (0.52-1.22) for DHA. Results were adjusted for parity, smoking status, alcohol intake, BMI, medication, occupation, physical activity, marital status and having pregnancy-associated nausea.</p>	8
Rees et al., 2009, Australia	<p>Case-control, <b>n = 16:</b> <math>32.4 \pm 4.8</math>; control group = <math>33.13 \pm 3.3</math> yr</p>	<p>Cases met the criteria of one episode of major depression by DSM-IV criteria, and confirmed by both CIDI structured interview and psychiatrist clinical assessment, or scored <math>\geq 13</math> in EPDS, or <math>&gt; 14</math> in HDRS or <math>&gt; 25</math> in MADRS in the third trimester.</p>	<p>In plasma (%): for case group total <math>\omega</math>-3 PUFA = <math>6.9 \pm 1.5</math>, ALA = <math>0.2 \pm 0.1</math>, DHA = <math>5.0 \pm 1.5</math>, EPA = <math>0.6 \pm 0.3</math>, total <math>\omega</math>-6 PUFA = <math>33.9 \pm 2.2</math>, AA = <math>9.8 \pm 1.6</math> and DPA = <math>0.5 \pm 0.2</math>; for control group total <math>\omega</math>-3 PUFA = <math>8.1 \pm 1.9</math>, ALA = <math>0.2 \pm 0.1</math>, DHA = <math>6.3 \pm 1.4</math>, EPA = <math>0.7 \pm 0.5</math>, total <math>\omega</math>-6 PUFA = <math>32.3 (2.6)</math>, AA =</p>	<p>ORs (95% CI) of depression in third trimester were for high (&gt;median) vs. low plasma fatty acids levels: 0.21 (0.05-0.99) for total <math>\omega</math>-3 PUFA, 1.45 (0.33-6.50) for ALA, 0.18 (0.04-0.88) for DHA, 1.55 (0.34-7.08) for EPA, 2.28 (0.49-10.55) for total <math>\omega</math>-6 PUFA,</p>	8

			9.5 ± 5.4 and DPA = 0.6 ± 0.3 at third trimester.	2.73 (0.52–14.40) for AA, 1.74 (0.40–7.64) for DPA, 4.69 (1.00–21.99) for ω-6/ω-3, 0.75 (0.16–3.58) for AA/EPA, (0.47 (0.10–2.14) for DHA/DPA. Results were adjusted for age, education and parity.	
Mattes et al., 2009, Australia	Cross-sectional, <b>n</b> = 81, 31.7 ± 3.8 yr	22.2% scored ≥ 10 in BDI at 20 <sup>th</sup> gw.	In red blood cell (%), for BDI < 10: total ω-3 PUFA = 16.1 ± 1.6 and total ω-6 PUFA = 25.3 ± 1.3; for BDI ≥ 10: total ω-3 PUFA = 15.4 ± 2.0 and total ω-6 PUFA = 26.0 ± 1.2 at 20 <sup>th</sup> gw.	β <sub>logistic regression</sub> of depression as BDI scored ≥ 10 at 20 <sup>th</sup> wk were -0.29 ( <i>P</i> = 0.10), 0.45 ( <i>P</i> = 0.051) and -6.52 ( <i>P</i> = 0.06) for a 1-unit increment of red blood cell total ω-3 PUFA, total ω-6 PUFA and ω-3/ ω-6 ratio, respectively. Results were adjusted for maternal age, education and parity.	7
Shiraishi et al., 2015, Japan	Cross-sectional, <b>n</b> = 329, 34.7 ± 4.01 yr	5.8% scored > 8 in the Japanese version of EPDS at 19 <sup>th</sup> -23 <sup>th</sup> gw.	In plasma (μg/ml): for EPDS > 8 EPA = 21 (13–39) and DHA = 107 (81–128); for EPDS ≤ 8 EPA = 25 (17–38) and DHA = 125 (105–148) at 19 <sup>th</sup> -23 <sup>th</sup> gw.	β <sub>logistic regression</sub> of depression as EPDS scored > 8 in middle pregnancy were -1.064 ( <i>P</i> = 0.28) and -4.894 ( <i>P</i> = 0.01) for a 1-unit increment of plasma EPA and DHA levels, respectively. Results were adjusted for age and the presence of pregnancy-associated nausea.	6
Vaz et al., 2014, Brazil <sup>1</sup>	Cross-sectional, <b>n</b> = 194, range 20–40 yr	17% major depressive episode by Mini International Neuropsychiatric Interview DSM-	In serum (%): LA = 30.8 ± 3.4, AA = 9.2 ± 1.6, AdA = 0.38 ± 0.09, ω-6 HUFA = 78.2 ± 3.8, ALA = 0.62 ±	ORs (95% CI) of major depressive episode in the first trimester for an increase in 1-	7

<p>Verly-Miguel et al., 2015, Brazil<sup>1</sup></p>	<p>Cross-sectional, <b>n = 228</b>, range 20–40 yr</p>	<p>IV at 6<sup>th</sup>-13<sup>th</sup> gw. 25% of at least one anxiety disorder by Mini International Neuropsychiatric Interview DSM-IV at 5<sup>th</sup>-13<sup>th</sup> gw.</p>	<p>0.13, EPA= 0.42 ± 0.21, ω-3 DPA= 0.53 ± 0.10, DHA= 2.4 ± 0.5, ω-3 HUFA = 21.7 ± 3.8, total MUFA = 20.5 ± 2.2 and total SFAs= 31.9 ± 1.6 at 6<sup>th</sup>-13<sup>th</sup> gw.</p> <p>In serum (μg/mL): ALA, EPA, ω-3 DPA, DHA, total ω-3 PUFA, LA, AA, AdA and total ω-6 PUFA (NR means) at 5<sup>th</sup>-13<sup>th</sup> gw (NR means).</p>	<p>unit of z score of serum fatty acids levels were: 0.74 (0.52-1.06) for LA, 1.47 (1.03-2.10) for AA, 1.59 (1.09-2.32) for AdA, 1.25 (0.82-1.90) for ω-6 HUFA, 0.80 (0.56-1.14) for ALA, 1.02 (0.69-1.40) for EPA, 1.01 (0.70-1.47) for ω-3 DPA, 1.06 (0.72-1.55) for DHA, 0.80 (0.52-1.21) for ω-3 HUFA, 1.14 (0.79-1.64) for total MUFA and 1.10 (0.76-1.58) for total SFA. Results were adjusted for marital status, current smoking habit, close relatives and gw.</p> <p>ORs (95% CI) of anxiety disorders in the first trimester for the lowest tertile of serum fatty acids levels were: 1.27 (0.64-2.55) for ALA, 0.93 (0.48-1.82) for EPA, 1.18 (0.61-2.27) for ω-3 DPA, 1.95 (1.00-3.77) for DHA, 1.76 (0.91-3.40) for total ω-3 PUFA, 1.47 (0.76-2.84) for LA, 0.93 (0.47-1.82) for AA, 0.98 (0.48-1.97) for AdA, 1.03 (0.53-2.01) for total ω-6 PUFA, 1.53 (0.79-2.95) for ω-6/ ω-3. Results were adjusted for</p>
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parity, per-capita family income, early pregnancy body mass index and gestational age at the blood sampling.

# Outcomes in postpartum

Markhus et al., 2013, Norway <sup>3</sup>	Cohort, <b>n = 44</b> , 29.5 ± 5.0 yr	6.9% scored ≥ 10 in Norwegian version EPDS at third postnatal mo.	In red blood cell (%): total SFA = 39.2 ± 2.5, total MUFA = 18.7 ± 2.0, AA= 11.2 ± 1.7, ALA= 0.3 ± 0.1, EPA= 0.7 ± 0.4, DPA= 1.7 ± 0.5, DHA= 5.7 ± 1.4 at 28 <sup>th</sup> gw.	Pearson correlations between EPDS score and red blood cell fatty acids levels were: 0.12 ( <i>P</i> = 0.43) for total SFAs, 0.20 ( <i>P</i> = 0.20) for total MUFAs, -0.20 ( <i>P</i> = 0.21) for AA, 0.08 ( <i>P</i> = 0.59) for ALA, -0.26 ( <i>P</i> = 0.10) for EPA, -0.35 ( <i>P</i> = 0.02) for DPA, 0.41 ( <i>P</i> = 0.006) for DHA, 0.31 ( <i>P</i> = 0.04) for ω-3/ω-6 ratio.	5
Otto et al., 2003, Netherlands	Cohort, <b>n = 112</b> , 30.66 ± 3.28 yr	21% scored ≥ 10 in Dutch version EPDS at 32 <sup>th</sup> postnatal wk.	In plasma (%) at delivery for ω-3 DHA= 3.91 ± 0.94, ω-6 DPA= 0.47 ± 0.19, also measured at 32 <sup>th</sup> postnatal wk (NR %).	Spearman correlation between EPDS score and plasma fatty acids levels were: (a) at delivery: - 0.06 ( <i>P</i> = 0.563) for DHA, -0.01 ( <i>P</i> = 0.927) for ω-6 DPA, -0.01 ( <i>P</i> = 0.91) for DHA/ω-6 DPA; (b) Postnatal change (difference between at delivery and 32 <sup>th</sup> postnatal wk values): 0.04 ( <i>P</i> = 0.694) for DHA, 0.04 ( <i>P</i> = 0.681) for DPA, -0.08 ( <i>P</i> = 0.43) for DHA/ω-6 DPA.	6

Parker et al., 2015, Australia	Cohort, <b>n = 895</b> , 31.0 ± 5.7 yr	19.8% at 36 <sup>th</sup> gw and 17.8% third postnatal mo scored ≥ 10 in EPDS.	In red blood cell (%): total SFA = 44.8 ± 1.3, total ω-6 PUFA = 26.8 ± 1.8, total ω-3 PUFA = 9.3 ± 1.7, ω-3 DHA = 6.1 ± 1.2, ω-3 DPA = 2.2 ± 0.3, EPA = 0.58 ± 0.37 and AA = 11.8 ± 1.0 at 36 <sup>th</sup> gw.	OR of depression as EPDS score ≥ 10 was 0.88 ( <i>P</i> = 0.03) for 1-unit increase of postnatal change for plasma DHA/ω-6 DPA. Results were adjusted for parity, educational level, maternal age at test moment, breast/bottle-feeding, smoking and alcohol use.	Pearson's correlations between third postnatal mo EPDS scores and red blood cell fatty acids levels were: 0.003 for total SFAs, 0.03 for total ω-6 PUFA, -0.017 for total ω-3 PUFA, 0.020 for ω-6/ω-3, -0.012 for ω-3 DHA, -0.019 for ω-3 DPA, -0.025 for EPA, -0.016 for DHA+EPA, -0.023 for AA. All correlations presented <i>P</i> > 0.05.	ORs of depression as EPDS score ≥ 10 were 1.1 ( <i>P</i> < 0.05) for lower total ω-3 PUFA, 2.7 ( <i>P</i> < 0.05) for lower EPA and 1.1 ( <i>P</i> < 0.05) for higher total ω-6 PUFAs levels. Results were adjusted for neuroticism scores, stress during pregnancy, a
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				lifetime depressive episode and older age.
				$\beta$ linear regression of anxiety scores were for log-transformed plasma fatty acids levels: -6.49 ( $P = 0.019$ ) for total $\omega$ -3 PUFA, 5.03 ( $P = 0.196$ ) for total $\omega$ -6 PUFAs (these last two were analyzed in the same model), 6.58 ( $P = 0.017$ ) for $\omega$ -6/ $\omega$ -3, 7.54 ( $P = 0.004$ ) for AA/DHA, 3.44 ( $P = 0.013$ ) for AA/EPA, 5.36 ( $P = 0.025$ ) for AA/DPA, 5.62 ( $P = 0.061$ ) for AA/DHA, 1.96 ( $P = 0.269$ ) for AA/EPA and 0.95 ( $P = 0.765$ ) for AA/DPA (these last three were analyzed in the same model) at 26 <sup>th</sup> -28 <sup>th</sup> gw. For third postnatal mo were for log-transformed fatty acids levels: -0.42 ( $P = 0.874$ ) for total $\omega$ -3 PUFA, 0.25 ( $P = 0.948$ ) for total $\omega$ -6 PUFA (these last two were analyzed in the same model), 0.44 ( $P = 0.870$ ) for $\omega$ -6/ $\omega$ -3, 0.63 ( $P = 0.805$ ) for AA/DHA, -0.50 ( $P = 0.708$ ) for AA/EPA, -0.72 ( $P = 0.753$ ) for AA/DPA,
Chong et al., 2015, Singapore <sup>4</sup>	Cohort, $n = 698$ , 30.8 $\pm$ 5.2 yr	7.2% scored $\geq$ 15 in the EPDS at 26 <sup>th</sup> -28 <sup>th</sup> gw and 10.3% scored $\geq$ 13 in the EPDS at the third postnatal mo. Anxiety by STAI-state subscale at same time.	In plasma ( $\mu\text{g/mL}$ ): total $\omega$ -3 PUFA = 142.4 (36.2-690.4) and $\omega$ -6 PUFA = 799.4 (271.8-2.186.3) at 26 <sup>th</sup> -28 <sup>th</sup> gw.	9

1.38 ( $P = 0.633$ )  
for AA/DHA, -  
0.51 ( $P = 0.763$ )  
for AA/EPA and  
-0.75 ( $P =$   
0.805) for  
AA/DPA (these  
last three were  
analyzed in the  
same model).

ORs (95% CI)  
of depression for  
log-transformed  
fatty acids levels  
were: 1.40  
(0.29-6.73) for  
total  $\omega$ -3 PUFA,  
4.48 (0.51-  
39.68) for total  
 $\omega$ -6 PUFA, 2.75  
(0.27-27.87) for  
 $\omega$ -6/  $\omega$ -3, 1.71  
(0.18-16.02) for  
AA/DHA, 1.66  
(0.52-5.36) for  
AA/EPA, 2.36  
(0.32-17.37) for  
AA/DPA; and  
1.05 (0.08-  
13.44) for  
AA/DHA, 1.38  
(0.31-6.18) for  
AA/EPA, 1.65  
(0.12-23.39) for  
AA/DPA (these  
last three were  
analyzed in the  
same model) at  
26<sup>th</sup>-28<sup>th</sup> gw. For  
third postnatal  
mo were: 1.48  
(0.40-5.55) for  
total  $\omega$ -3 PUFA,  
1.63 (0.24-  
10.97) for total  
 $\omega$ -6 PUFA, 0.70  
(0.09-5.14) for  
 $\omega$ -6/  $\omega$ -3, 0.90  
(0.13-6.32) for  
AA/DHA, 0.80  
(0.30-2.13) for  
AA/EPA, 1.73  
(0.30-10.04) for  
AA/DPA, 0.74  
(0.08-6.69) for  
AA/DHA, 0.54  
(0.16-1.85) for  
AA/EPA, 3.81  
(0.39-37.06) for  
AA/DPA (these

<p>Sallis et al., 2014, United Kingdom<sup>5</sup></p>	<p>Cohort, <b>n =</b> <b>3,397</b>, 28.9 ± 4.5 yr</p>	<p>11.5% perinatal onset of depression defined as scored &gt; 12 in the EPDS at 32<sup>th</sup> gw and 8<sup>th</sup> postnatal wk (without diagnosing at 18<sup>th</sup> gw).</p>	<p>In red blood cell (%): EPA = 0.27 ± 0.16 and DHA = 2.31 ± 1.33 after 20<sup>th</sup> gw.</p>	<p>last three were analyzed in the same model). All results were adjusted for ethnicity, parity, education level, marital status, maternal body mass index at 26<sup>th</sup>-28<sup>th</sup> gw, maternal age, employment status, maternal and infant health status, smoking status, alcohol consumption, history of abortion, miscarriage and stillbirth, frequency of exercise, and reported fish oil supplementation. For third postnatal mo, results were further adjusted infant sex, mode of delivery, and respective STAI or EPDS scores at 26<sup>th</sup>-28<sup>th</sup> gw.</p> <p>ORs (95% CI): a) of perinatal onset for red blood cell fatty acid levels were: 1.07 (0.99-1.15) for EPA and 1.08 (0.98-1.19) for DHA; b) of antenatal depression were: 0.97 (0.91-1.04) for EPA and 0.99 (0.91-1.07) for DHA; c) of postnatal depression were 1.04 (0.96-1.13) for EPA and 1.04 (0.94-1.15) for DHA. All results were adjusted for social class and</p>
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maternal age.

# CHOLESTEROL

## Outcomes in pregnancy

Teofilo et al., 2014, Brazil <sup>1, 6</sup>	Cohort, <b>n = 238</b> , range 20–40 yr	34.4% scored $\geq$ 11 in the Brazilian version of EPDS at 5 <sup>th</sup> -13 <sup>th</sup> gw, 21.5% at 20 <sup>th</sup> -26 <sup>th</sup> gw and 21.5% at 30 <sup>th</sup> -36 <sup>th</sup> gw.	Serum HDL-cholesterol mean (95% CI) 47.7 (46.5-49.0) for EPDS < 11 and 47.5 (45.7-49.3) (mg/dL) for EPDS $\geq$ 11 at 5 <sup>th</sup> -13 <sup>th</sup> gw. It was also measured at 20 <sup>th</sup> -26 <sup>th</sup> and 30 <sup>th</sup> -36 <sup>th</sup> gw.	$\beta_{\text{longitudinal linear regression}}$ (95% CI) was -0.080 (-0.157-0.002, $P = 0.043$ ) for a 1-unit increase of serum HDL-cholesterol when longitudinal changes throughout pregnancy of EPDS scores. Results were adjusted for age, education, marital status, physical activity, work outside home, parity, unplanned pregnancy, generalized anxiety disorder, current suicidal ideation, global physical violence, LDL-Cholesterol, pre-pregnancy BMI and gestational age.
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## Outcomes in postpartum

Ploekinger et al., 1996, Italy	Cohort, <b>n = 20</b> , 25.3 3.7 yr	Means $\pm$ SD: day -14 = 33.8 $\pm$ 7.3, 1 <sup>st</sup> day postnatal = 33.6 $\pm$ 8.0, 2 <sup>nd</sup> day = 32.1 $\pm$ 7.6, 3 <sup>rd</sup> day = 30.0 $\pm$ 7.3, 4 <sup>th</sup> day = 29.7 $\pm$ 7.9 by Zung self-rating depression scale at second wk before the expected delivery and daily from the 1 <sup>st</sup> to 4 <sup>th</sup> postnatal day.	Serum cholesterol = 6.52 $\pm$ 1.19 at second wk before the expected delivery, 5.40 $\pm$ 0.88 at first postnatal day and 5.92 $\pm$ 1.58 (mmol/L) at third postnatal day.	Pearson correlations between the Zung self-rating scale scores (assessed in postnatal days 1-4) and relative changes in serum cholesterol from pre-partum to postnatal were: (a) from second wk before delivery to first postnatal day for cholesterol
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van Dam et al., 1999, Netherlands <sup>7</sup>	Cohort, <b>n = 305</b> , 29 ± 3.3 yr	23.6% with depression by Research Diagnostic Criteria at 10 <sup>th</sup> - 34 <sup>th</sup> postnatal wk.	Serum cholesterol at 32 <sup>th</sup> gw and 10 <sup>th</sup> postnatal wk (NR means).	measurements: - 0.30 ( <i>P</i> = 0.47) on day 1, -0.73 ( <i>P</i> = 0.02) on day 2, -0.73 ( <i>P</i> = 0.02) on day 3, and -0.68 ( <i>P</i> = 0.03) on day 4; (b) from second wk before delivery to third postnatal day for cholesterol measurements: - 0.75 ( <i>P</i> = 0.01) on day 2, -0.74 ( <i>P</i> = 0.01) on day 3 and -0.63 ( <i>P</i> = 0.05) on day 4.  OR (95% CI) of depression between the 10 <sup>th</sup> -32 <sup>th</sup> postnatal wk for the highest (> 1.6 mmol/l) versus lowest tertiles (< 0.9 mmol/l) of serum cholesterol decline was 1.4 (0.64-2.9). Results were adjusted for age, parity, education level, smoking status, concurrent illness, and social support.	8
Grussu et al., 2007, Italy <sup>8</sup>	Cross- sectional, <b>n = 209</b> , range 25 – 41 yr	Mean ± SD Depression = 2.5 ± 2.8 by Kellner Symptom Questionnaire at third postnatal day.	Serum cholesterol = 6.3 ± 1.4 (mmol/L) at third postnatal day.	Spearman correlation between the serum cholesterol levels and depression scale scores was -0.15 ( <i>P</i> < 0.05) in third postnatal day.	5

**Outcomes in pregnancy and  
postpartum**

Troisi et al., 2002, Italy	Cohort, $n = 47$ , 29.4 $\pm$ 3.8 yr	Mean $\pm$ SD: in late pregnancy: STAI = 33.30 $\pm$ 7.41 and BDI = 7.32 $\pm$ 3.13. In early postnatal: STAI = 33.85 $\pm$ 8.45 and BDI = 6.64 $\pm$ 5.10.	In serum (mg/dL): total cholesterol = 290.91 $\pm$ 44.40 and HDL-cholesterol = 71.13 $\pm$ 17.97 at late pregnancy (median = -20 day before expected delivery, range: -52- -1); total cholesterol = 235.19 $\pm$ 43.69 and HDL-cholesterol = 62.75 $\pm$ 13.78 at early postnatal (median = 32 day after delivery, range: 16-56).	Pearson correlations were: (a) Antenatal: between serum total cholesterol and STAI -0.04 ( $P = 0.77$ ), and BDI -0.19 ( $P = 0.21$ ); between HDL-cholesterol and STAI -0.15 ( $P = 0.33$ ), and BDI -0.29 ( $P = 0.053$ ). (b) Postnatal: between total cholesterol and STAI -0.29 ( $P = 0.05$ ), and BDI -0.34 ( $P = 0.02$ ); between HDL-cholesterol and STAI -0.34 ( $P = 0.02$ ), and BDI -0.25 ( $P = 0.10$ ); c) between relative changes in total cholesterol levels from antenatal to postnatal and postnatal STAI 0.15 ( $P = 0.33$ ), and postnatal BDI -0.26 ( $P = 0.08$ ). All results were adjusted for the day of assessment before delivery.	4
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**Patterns of fatty acids, carotenoids and micronutrients and outcome in pregnancy**

Bodnar et al., 2012, USA <sup>9</sup>	Cohort, $n = 135$ , range 18-43 yr	21.5% major depressive disorder by Structured Clinical Interview for DSM-IV at 20 <sup>th</sup> , 30 <sup>th</sup> and 36 <sup>th</sup> gw.	In red blood cell (%): DHA = 2.80 (2.36-3.33), AA = 11.8 (10.7-13.1), EPA = 0.30 (0.26-0.34). In plasma geometric mean (95% CI) (nmol/L): folate = 31.5 (28.9-34.3), ascorbic acid = 66.1 (61.6-70.8),	ORs (95% CI) of major depressive disorder during pregnancy (3 points) were 0.8 (0.3-2.1), 1.4 (0.5-3.8) and 0.8 (0.3-2.1) in the highest versus lowest tertiles of essential fatty acids, micronutrients	7
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Hcy = 2.32 (2.17-2.48) (μmol/L). In serum geometric mean (95% CI) (nmol/L): retinol = 1649 (1580-1721), 25-hydroxyvitamin D = 81.9 (75.1-89.3), α-tocopherol = 161 (156-165), β-carotene = 162 (127-206), Lutein+zeaxanthin = 102 (90.5-114), β-cryptoxanthin = 132 (110-158), lycopene = 541 (489-598), soluble transferrin receptors = 15.6 (14.5-15.9) (μmol/L). All biomarkers were measured at ≤ 20 gw. and carotenoids scores, respectively, adjusted for study visit number, employment, education and pre-pregnancy BMI.

**Abbreviations:** AA = arachidonic acid; AdA = adrenic acid; ALA = α-linolenic acid; BDI = Beck Depression Inventory; CI = confidence interval; CIDI = Composite International Diagnostic Interview; DHA = docosahexaenoic acid; DMS-IV = Diagnostic and Statistical Manual of Mental Disorders; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; EPDS = Edinburgh Postnatal Depression Scale; gw = gestational week; h = hour; HDRS = Hamilton Depression Rating scale; HUFA = highly unsaturated fatty acids; IR = interquartile range; LA = linoleic acid; MADRS = Montgomery-Asberg Depression Rating Scale; mo = month; MUFA = monounsaturated fatty acids; NOS = Newcastle-Ottawa scale; NR = not reported; PUFA = polyunsaturated fatty acids; SD = standard deviation; SFA = saturated fatty acids; STAI = Spielberger's State-Trait Anxiety Index; wk = week; yr = year.

<sup>1</sup> These studies were based on data from the same primary research.

<sup>2</sup> Enrollment and follow-up lasted between November 2009 and July 2012.

<sup>3</sup> Women reported to consume ω3 supplements on average  $4.9 \pm 3.0$  times per week.

<sup>4</sup> Participants were Singaporean citizens or permanent residents of Chinese, Malay or Indian ethnicity with parents of homogenous ethnicity background. 93.1% and 93.0% of women took folic acid and vitamin B<sub>12</sub> supplements, respectively.

<sup>5</sup> Women included in the analysis were of self-reported White European ethnicity.

<sup>6</sup> A subsample of 41 women participated in a clinical trial of treatment of 1.08 g EPA+ 0.72 g DHA per day and placebo for 16 weeks after the 22<sup>th</sup>-24<sup>th</sup> gestation week (this sample was excluded in Pinto et al., 2016).

<sup>7</sup> Participants were white women.

<sup>8</sup> The sample size was 356 women, but only 209 mothers were in the traditional after-delivery nursing care group showed data of interest.

<sup>9</sup> Bodnar et al., 2012 studied several biomarkers simultaneously by estimating factor scores for fatty acids, micronutrients and carotenoids.

**Table 3.** Characteristics of included studies evaluating the associations between micronutrients and amino acids and psychological distress in women during pregnancy and the first postpartum year.

Study, country	Study design, sample size and age (mean $\pm$ SD)	Psychological distress (% assessment tool, timing)	Nutritional biomarker (sample, mean $\pm$ SD or median (IR), timing)	Main results	NOS scores
<b>VITAMIN D</b>					
<b>Outcomes in pregnancy</b>					
Brandenburg et al., 2012, Netherlands <sup>1</sup>	Cohort, <b>n = 4,101</b> , 31.0 $\pm$ 4.8 yr	28% scored $\geq$ 16 in CESD scale at median (IR) = 16 <sup>th</sup> (14 <sup>th</sup> -18 <sup>th</sup> ) gw.	Serum vitamin D = 57.0 $\pm$ 30.8 (nM) at median (IR) = 13 (12-14) gw.	ORs (95% CI) of high levels of depressive symptoms (scored $\geq$ 16 CESD) in middle pregnancy were 1.48 (1.13-1.95), 1.44 (1.12-1.85), 1.21 (0.97-1.51) for women in the deficient (< 29 nM), insufficient (between 30-49.9 nM) and sufficient (50-79.9 nM) categories of serum vitamin D levels, respectively, in relation to normal as reference ( $\geq$ 80 nM). Results were adjusted for maternal age, parity and ethnicity, life-style, psychosocial and sociodemographic variables.	8
Cassidy-Byshrow et al., 2012, USA <sup>2, 3, 4, 5</sup>	Cohort, <b>n = 178</b> , 26.7 $\pm$ 6.0 yr	41.6% scored $\geq$ 16 in CESD scale at mean (SD) = 20.8 (3.7) gw.	Serum vitamin D = 13.4 $\pm$ 8.4 (ng/mL) at mean $\pm$ SD = 9.5 $\pm$ 3.6 gw.	OR (95% CI) of CESD score $\geq$ 16 in pregnancy was 0.54 (0.29-0.99) per unit increase of log-transformed	8

				<p>serum vitamin D levels in women. Results were adjusted for maternal age, high-school education, marital status, season of vitamin D measurement, and number of days between vitamin D and CESD measures.</p>
<p>Huang et al., 2014, USA <sup>6</sup></p>	<p>Cross-sectional, <b>n = 498</b>, 33.4 ± 4.2 yr</p>	<p>12.2% scored &gt; 10 for depression in PHQ-9, 12.4% scored &gt; 10 for anxiety in DASS and 7.6% scored &gt; 19 for stress in DASS at mean = 15.4 ± 2.6 gw.</p>	<p>Serum vitamin D = 34.4 ± 8.7 (ng/mL) at mean ± SD 15.4 ± 2.6 gw.</p>	<p><math>\beta_{\text{linear regression}}</math> were: 0.017 (<math>P = 0.547</math>) for increase in DASS-21 depression score, 0.019 (<math>P = 0.398</math>) for difference in DASS-21 anxiety score, 0.037 (<math>P = 0.281</math>) for difference in DASS-21 stress score, 0.019 (<math>P = 0.335</math>) for difference in PHQ-9 per 1 ng/ml decrease in serum vitamin D during pregnancy. All results were adjusted for season, gestational age at blood draw, age at enrolment, pre-pregnancy BMI, smoking status, white race, education and marital status.</p>

# Outcomes in postpartum

<p>Accort et al., 2016, USA <sup>2, 3, 4, 7</sup></p>	<p>Cohort, <b>n = 91</b>, 26.0 ± 6 yr</p>	<p>12% scored ≥12 in the EPDS score at 4<sup>th</sup>-6<sup>th</sup> postnatal wk (mean = 4.5 ± 1.8).</p>	<p>Serum vitamin D= 13.2 ± 9.4 (ng/mL) at first prenatal visit (mean = 9.7 ± 3.7 gw).</p>	<p><math>\beta_{\text{linear regression}}</math> was -0.209 (<math>P = 0.058</math>) for EPDS score 3-4<sup>th</sup> postnatal wk by a 1-unit increase of log-transformed serum vitamin D levels. Results were adjusted for maternal age, education, marital</p>
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				status, history of depression, season of vitamin D measurement and pre-pregnancy BMI.	
				OR (95% CI) of depression (as scored $\geq 12$ in EPDS) at third postnatal mo was 0.81 (0.70-0.92) by a 1-unit increase of serum vitamin D levels. Results were adjusted for age, breastfeeding, stressful life events, maternal education, family income, partner support, planned versus unplanned pregnancy, mode of delivery and previous psychiatric contact.	
Fu et al., 2015, China <sup>8</sup>	Cohort, <b>n</b> = 213, mean (IR) = 31 (29-32) yr	12.2% scored $\geq 12$ in Chinese version of EPDS at third postnatal mo.	Serum vitamin D median (IR) = 13.8 (9.4-17.1) (ng/mL) at 24-48 postnatal h.		7
Gur et al., 2014, Turkey <sup>9,10, 11</sup>	Cohort, <b>n</b> = 208, 28.5 yr	21.1% at first postnatal wk, 23.2% at 6 <sup>th</sup> wk and 23.7% at 6 <sup>th</sup> mo scored $\geq 12$ in EPDS.	Serum vitamin D = $22.4 \pm 11.2$ (ng/mL) at 24 <sup>th</sup> -28 <sup>th</sup> gw.	Pearson correlations between serum vitamin D levels and EDPS scores were: -0.2 ( $P$ = 0.02), -0.2 ( $P$ = 0.01) and -0.3 ( $P$ < 0.01) at first postnatal wk, 6 <sup>th</sup> wk and 6 <sup>th</sup> mo, respectively.	6
Robinson et al., 2014, Australia <sup>12</sup>	Cohort, <b>n</b> = 929, NR mean age	Postnatal depression symptoms: None symptoms = 28.0%, 1-5 symptoms = 50.4%, 6+ symptoms = 21.5% by six questions derived from the EPDS in third postnatal day.	Serum vitamin D at 18 <sup>th</sup> gw (NR means).	ORs (95% CI) of women with more than 6 depression symptoms in EDPS score in the third postnatal day were 2.72 (1.42-5.22), 1.37 (0.71-2.63), 1.61 (0.83-3.10) in the first (<47 nmol/L), second and third in relation to the fourth (>70 mmol/L) quartile	8

of serum vitamin D levels. Results were adjusted for pre-pregnancy body mass index, maternal age, maternal education, total family income, maternal smoking, maternal alcohol intake, hypertensive diseases of pregnancy, proportion of optimal birth weight, child sex, special care nursery admission and season of birth.

## VITAMIN B and AMINO ACIDS

### Outcomes in pregnancy

Watanabe et al., 2010, Japan <sup>13</sup>	Cross-sectional, $n = 86$ , 30.9 $\pm$ 4.6 yr	61.6% scored $\geq 16$ in Japanese version CESD at 6 <sup>th</sup> -11 <sup>th</sup> gw.	Serum folate: median (IR) <sub>non-depressed</sub> = 8.0 (5.5), median (IR) <sub>depressed</sub> = 8.2 (4.5) (ng/mL); plasma Hcy : median (IR) <sub>non-depressed</sub> = 6.0 (2.4), median(IR) <sub>depressed</sub> = 6.1 (1.4) at 4 <sup>th</sup> -11 <sup>th</sup> gw.	ORs (95% CI) of depression as scored $\geq 16$ in CESD at first trimester were 0.63 (0.24-1.61) and 0.63 (0.23-1.72) in women with serum folate levels < 8.1 ng/mL and Hcy levels $\geq 6.1$ mmol/mL, respectively. Results were adjusted for parity, number of vomits/day and gestational age.	6
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### Outcomes in postpartum

Blunden et al., 2012, United Kingdom <sup>14, 15</sup>	Cohort, $n = 2,856$ , NR mean age	32% scored $> 13$ in EPDS at 6 <sup>th</sup> -12 <sup>th</sup> postnatal mo.	Red blood cell folate geometric mean (95% CI) = 2413 (2365-2461) (nmol/L) at 11 <sup>th</sup> gw.	RR (95% CI) of depression as EPDS score $\geq 13$ at 6-12 <sup>th</sup> postnatal mo was 1.0 (1.0-1.0) for an increase of 10 units in the red blood cell folate	6
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				levels.	
Handley et al., 1977, United Kingdom	Cohort, <b>n = 18</b> , range 18- 31 yr	NR %, diagnosed by MAACL at 2 <sup>nd</sup> -5 <sup>th</sup> postnatal day.	Plasma free Trp, mean $\pm$ SE = 6.9 $\pm$ 1.4, 8.0 $\pm$ 0.7, 7.9 $\pm$ 0.5, 9.0 $\pm$ 0.7 ( $\mu$ mol/L) at 2 <sup>nd</sup> -5 <sup>th</sup> postnatal day.	Spearman's correlation between MAACL depression score at 2-5 <sup>th</sup> postnatal day and plasma free Trp levels was -0.3 ( $P$ < 0.01).	4
Handley et al., 1980, United Kingdom	Cohort, <b>n = 71</b> , range 17- 39 yr	39% scored at least one of the scales on $\geq$ 11 Blues index, $\geq$ 15 BDI, $\geq$ 22 MAACL and $\geq$ 7 VAS at 1 <sup>st</sup> -5 <sup>th</sup> postnatal day.	Plasma total Trp at first postnatal day (NR means).	Spearman's correlation between BDI score at 1-5 <sup>th</sup> postnatal day and plasma Trp levels was -0.2069 ( $P$ = 0.141).	6
Stein et al., 1976, United Kingdom	Cohort, <b>n = 18</b> , mean $\pm$ SE = 27.4 $\pm$ 1.2 yr	Mean $\pm$ SE = 2.35 $\pm$ 0.42 of affective score by the rank number of symptoms (tearfulness, depression, anxiety, appetite and insomnia) in 7 <sup>th</sup> -8 <sup>th</sup> postnatal day.	Plasma total Trp mean $\pm$ SE = 84.7 $\pm$ 2.3 ( $\mu$ mol/L) at 6 <sup>th</sup> postnatal day.	Pearson correlation between depression symptoms at 7-8 <sup>th</sup> day postnatal and plasma free Trp levels was -0.60 ( $P$ < 0.01).	1
Abou-Saleh et al., 1999, United Arab Emirates	Cross- sectional, <b>n = 62</b> , 30.8 $\pm$ 6.2 yr	8% scored $\geq$ 11 in Arabic version of the EPDS at 7 <sup>th</sup> postnatal day.	In plasma, Met = 31.46 $\pm$ 15.40, Trp = 40.77 $\pm$ 12.48, Tyr = 72.28 $\pm$ 29.89, Phe = 65.18 $\pm$ 16.17 ( $\mu$ mol/L), and vitamin B <sub>12</sub> = 374.94 $\pm$ 152.2 (pg/mL) at 7 <sup>th</sup> postnatal day.	Pearson correlations between the EPDS scores at 7 <sup>th</sup> day postnatal and the levels of plasma biomarkers were: -0.44 ( $P$ < 0.001) for Met, -0.44 ( $P$ < 0.01) for Trp, - 0.41 ( $P$ < 0.01) for Tyr, 0.39 ( $P$ < 0.01) for vitamin B <sub>12</sub> , 0.35 ( $P$ < 0.01) for Phe/Tyr, -0.27 ( $P$ < 0.05) for Tyr/ (Val, Leu, Ile, Phe).	5
Maes et al.,	Cross- sectional,	(NR %) diagnosed by	In plasma, mean $\pm$ SE at third	Pearson correlation	5

1992, Belgium	<b>n = 29</b> , mean $\pm$ SE = 28.3 $\pm$ 0.7 yr	Zung Depression and Anxiety scale, BDI, and the STAI at third postnatal day.	postnatal day: Trp = 51.2 $\pm$ 1.8, Val = 193.6 $\pm$ 5.0, Leu = 142.1 $\pm$ 4.4, Ile = 67.7 $\pm$ 2.4 and Phe = 100.7 $\pm$ 4.0 (10 <sup>-6</sup> mol/L).	between plasma Trp/ (Val, Leu, Ile, Phe) and the Zung Depression, Zung Anxiety and STAI scores at third postnatal day were -0.46 ( <i>P</i> = 0.007), -0.51 ( <i>P</i> = 0.003) and - 0.53 ( <i>P</i> = 0.002), respectively.
<b>Outcomes in pregnancy and postpartum</b>				
Chong et al., 2014, Singapore 16	Cohort, <b>n = 967</b> , 30.7 $\pm$ 5.1 yr	7.2% scored in the EPDS $\geq$ 15 at 26 <sup>th</sup> -28 <sup>th</sup> gw and 10.4% scored $\geq$ 13 at third postnatal mo.	In plasma, folate = 40.4 (36.4) in EPDS < 15 and 27.3 $\pm$ 13.8 (nmol/L) in EPDS $\geq$ 15; vitamin B <sub>12</sub> = 220.1 $\pm$ 77.6 in EPDS < 15 and 211.2 $\pm$ 66.0 (pmol/L) in EPDS $\geq$ 15 at 26 <sup>th</sup> -28 <sup>th</sup> gw.	ORs (95% CI) of depression in antenatal period were 0.69 (0.52- 0.94) and 1.07 (0.79-1.45) for 1 SD increase in log-transformed plasma folate and vitamin B <sub>12</sub> levels, respectively. For postnatal period, ORs (95% CI) of depression were 0.75 (0.58-0.99) and 1.08 (0.83- 1.40) for 1 SD increase in log- transformed folate and vitamin B <sub>12</sub> levels, respectively. All analysis were adjusted for maternal age, ethnicity, educational level of the mother, gravidity, smoke exposure before and during pregnancy, alcohol consumption before pregnancy, variables associated with health status of mothers and children. Results of postnatal depression were further adjusted

Maes et al., 2001, Belgium	Cohort, <b>n = 98</b> , 27.8 ± 3.5 yr	21 women scored at the q75 values of changes in the STAI score from the 3 <sup>rd</sup> - 6 <sup>th</sup> day before the delivery, first postnatal day, to third postnatal day.	Plasma Phe = 86.1 ± 16.8 at 3 <sup>rd</sup> - 6 <sup>th</sup> day before the delivery, 101.9 ± 24.9 at first postnatal day and 110.0 ± 22.9 (μmol/L) and third postnatal day.	by previous depressive symptoms.  Pearson correlation between the changes of STAI score and changes in plasma Phe levels was 0.16 ( <i>P</i> = 0.04) from 3 <sup>rd</sup> - 6 <sup>th</sup> day before the delivery to first and third postnatal day.
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## FERRITIN

### Outcomes in postpartum

Albacar et al., 2011, Spain <sup>17, 18</sup>	Cohort, <b>n = 729</b> , 31.7 ± 4.7 yr	9% scored > 9 on the Spanish version of EPDS at 8 <sup>th</sup> - 32 <sup>th</sup> postnatal wk.	Serum ferritin = 21.3 ± 13.5 (μg/L) at 48 postnatal h.	OR (95% CI) of depression scored > 9 on EPDS at 8- 32 <sup>th</sup> postnatal wk was 3.73 (1.84- 7.56) in women in the category of serum ferritin < 7.26 μg/L vs higher levels. Results were adjusted for employment status, c-reactive protein and transferrin saturation.	6
Armony-Sivan et al., 2012, China <sup>19</sup>	Cohort, <b>n = 567</b> , 24.6 ± 3.7 yr	24.5% at 24- 48 h after delivery and 20.3% at 6 <sup>th</sup> postnatal wk scored ≥ 10 in the Chinese version of EPDS.	Serum ferritin = 41.9 ± 35.3 at 13 <sup>th</sup> -20 <sup>th</sup> and 14.1 ± 13.8 (ng/mL) at 36 <sup>th</sup> gw.	Spearman correlations between serum ferritin in mid- or late pregnancy and EPDS scores after delivery or at 6 <sup>th</sup> postnatal wk were < 0.10 ( <i>P</i> > 0.05).	6

## ZINC

### Outcomes in pregnancy and postpartum

Roomruangwong et al., 2016, Thailand	Cohort, <b>n = 72</b> , no depression group =	HDRS, EPDS, BDI, and STAI at third trimester	Serum Zn <sub>no</sub> depression = 80.3 ± 14.7 and in depression = 71.3 ±	OR (95% CI) of prenatal depression as scored ≥ 11 on	5
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	29.6 ± 7.1; depression group = 27.5 ± 6.3 yr	and 4 <sup>th</sup> -6 <sup>th</sup> postnatal wk. Scores ≥ 11 on EPDS was considered as prenatal depression (NR %).	8.3 (µg/dL) at third trimester.	EPDS was 4.16 (1.42-12.22) for a 1-unit increase of the inverse of serum zinc levels. Results were adjusted for age, lifetime history of depression, premenstrual syndrome and anxiety disorders.
				Pearson correlations between serum zinc levels and scores were - 0.425 ( <i>P</i> < 0.001) for EPDS, -0.478 ( <i>P</i> < 0.001) for HDRS, -0.507 ( <i>P</i> < 0.001) for BDI and -0.042 ( <i>P</i> = 0.729) for STAI.
Wojcik et al., 2006, Poland	Cohort, <i>n</i> = 66, 31.0 ± 1.0 yr	42% and 29% scored in 9 ≥ self-rated EPDS at third and 30 <sup>th</sup> postnatal day, respectively.	Serum Zn, mean (SE) (mg/L) = 0.61 ± 0.01 at third postnatal day and 0.80 ± 0.02 at 30 <sup>th</sup> postnatal day.	Spearman correlation between EPDRS scores and serum Zn levels was - 0.2968 ( <i>P</i> = 0.014) at third and 30 <sup>th</sup> postnatal day.

**Abbreviations:** BDI = Beck Depression Inventory; CESD = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; DASS = Depression, Anxiety and Stress Scales; EPDS = Edinburgh Postnatal Depression Scale; gw = gestational week; Hcy = homocysteine; HDRS = Hamilton Depression Rating scale; h = hour; Ile = isoleucine; IR = interquartile range; Leu = leucine; log = logarithm; MAACL = Multiple Affect Adjective Check List; MADRS = Montgomery-Asberg Depression Rating Scale; Met = methionine; mo = month; NOS = Newcastle-Ottawa scale; NR = not reported; Phe = Phenylalanine; PHQ = Patient Health Questionnaire; SD = Standard deviation; SE = Standard Error; STAI = Spielberger's State-Trait Anxiety Index; Trp = tryptophan; Tyr = tyrosine; Val = valine; VAS = Visual Analogue scale; wk = week; yr = years; Zn = zinc.

<sup>1</sup> 23% of women had vitamin D deficiency (< 29 nM) and 21% had insufficiency (30-50 nM).

<sup>2</sup> These studies are based on data from the same primary research. Only African-American ethnicity women were selected to participate in the study.

<sup>3</sup> The study visits occurred between February 2009 and June 2010.

<sup>4</sup> Women had prenatal vitamin prescriptions (74% used 50,000 IU/ week after assessment and other women took in the prenatal period 400 IU of vitamin D).

<sup>5</sup> 43.3% were deficient (< 12 ng/mL), 31.7% inadequate (12-20 ng/mL) and 18.3% sufficient (20-30 ng/mL) in levels of vitamin D.

<sup>6</sup> 40% of women were insufficient/ deficient (< 32 ng/mL) and 4.2% deficient (< 20 ng/mL) in vitamin D levels.

<sup>7</sup> 85% of women had inadequacy/ deficiency (< 20 ng/mL) in vitamin D levels.

<sup>8</sup> 82.6% of women were deficient (< 20 ng/mL) in vitamin D levels. Participants were of Chinese family origin

<sup>9</sup> Study data were collected between June 2012 and October 2012.

<sup>10</sup> 7.6% of women used vitamin D supplement of 1,200 IU/ day at least 3 days weekly, 84.6% of 400 IU/ day and 7.6% never used.

<sup>11</sup> 11% of women had severe vitamin D deficiency (< 10 ng/mL) and 40.3% mild deficiency (10-20 ng/mL).

<sup>12</sup> Participants were of Caucasian ethnicity.

<sup>13</sup> Around 20% of women took vitamin supplements.

<sup>14</sup> 96.1% and 56.4 of women took acid folic and vitamin B supplements at 11 weeks.

<sup>15</sup> 1.44% and 0.32% of the women had marginal folate status (< 350 nmol/L) at baseline and pregnancy, respectively.

<sup>16</sup> Participants were Singaporean citizens or permanent residents of Chinese, Malay or Indian ethnicity with parents of homogenous ethnicity background. 93.1% and 93.0% of women took folic and vitamin B<sub>12</sub> supplements, respectively.

<sup>17</sup> The study was conducted between December 2003 and October 2004.

<sup>18</sup> Participants were of Caucasian ethnicity (only Spanish origin). 13.9% of women had marginal iron deficiency (ferritin < 12 µg/L and transferrin < 16%) and 24.7% suffered depletion of iron stores (ferritin < 12 µg/L).

<sup>19</sup> 30% of anemic women were iron deficient (soluble transferrin receptor/log ferritin index > 14) in middle pregnancy (*n* = 74 anemics) and 93% in late pregnancy (*n* = 141 anemics).

**Table 4.** Summary of the associations between the nutritional biomarkers and depression in women during pregnancy and the first postpartum year reported in at least two included studies.

Nutritional biomarker	Total of studies (reference) <sup>1</sup>	Number of studies with any significant association (reference) <sup>2</sup>
<b>Depression in pregnancy</b>		
AA	2 (Pinto et al., 2016,46, Vaz et al., 2014 56)	1 (Vaz et al., 2014)
Ada	2 (Pinto et al., 2016, Vaz et al., 2014)	1 (Vaz et al., 2014)
ALA	3 (Pinto et al., 2016, Rees et al., 2009, Vaz et al., 2014)	0
DHA	5 (Pinto et al., 2016, Rees et al., 2009, Sallis et al., 2014, Shiraishi et al., 2015, Vaz et al., 2014)	3 (Pinto et al., 2016, Rees et al., 2009, Shiraishi et al., 2015)
DPA (ω-3)	3 (Pinto et al., 2016, Rees et al., 2009, Vaz et al., 2014)	1 (Pinto et al., 2016)
EPA	5 (Pinto et al., 2016, Rees et al., 2009, Sallis et al., 2014, Shiraishi et al., 2015, Vaz et al., 2014)	1 (Pinto et al., 2016)
LA	2 (Pinto et al., 2016,46, Vaz et al., 2014)	0
total ω-6 PUFA	4 (Chong et al., 2015, Mattes et al., 2009, Pinto et al., 2016, Rees et al., 2009)	0
total ω-3 PUFA	4 (Chong et al., 2015, Mattes et al., 2009, Pinto et al., 2016, Rees et al., 2009)	2 (Pinto et al., 2016, Rees et al., 2009)
ω-6-PUFA/ω-3-PUFA	4 (Chong et al., 2015, Mattes et al., 2009, Pinto et al., 2016, Rees et al., 2009)	1 (Pinto et al., 2016)
AA/EPA	2 (Chong et al., 2015, Rees et al., 2009)	0
HDL-Cholesterol	2 (Teofilo et al., 2014, Troisi et al., 2002)	1 (Teofilo et al., 2014)

Vitamin D	3 (Brandenburg et al., 2012, Cassidy-Bushrow et al., 2012, Huang et al., 2014)	2 (Brandenburg et al., 2012, Cassidy-Bushrow et al., 2012)
Folate	2 (Chong et al., 2014, Watanabe et al., 2011)	1 (Chong et al., 2014)
<b>Depression in postpartum</b>		
AA	2 (Markhus et al., 2013, Parker et al., 2015)	0
DHA	4 (Markhus et al., 2013, Otto et al., 2003, Parker et al., 2015, Sallis et al., 2014)	1 (Markhus et al., 2013)
DPA ( $\omega$ -3)	3 (Markhus et al., 2013, Otto et al., 2003, Parker et al., 2015)	1 (Markhus et al., 2013)
EPA	3 (Markhus et al., 2013, Parker et al., 2015, Sallis et al., 2014)	1 (Parker et al., 2015)
total $\omega$ -6 PUFA	2 (Chong et al., 2015, Parker et al., 2015)	1 (Parker et al., 2015)
total $\omega$ -3 PUFA	2 (Chong et al., 2015, Parker et al., 2015)	1 (Parker et al., 2015)
$\omega$ -6-PUFA/ $\omega$ -3-PUFA	2 (Chong et al., 2015, Parker et al., 2015)	0
Total SFA	2 (Markhus et al., 2013, Parker et al., 2015)	0
Cholesterol	4 (Grussu et al., 2007, Ploekinger et al., 1996, Troisi et al., 2002, van Dam et al., 1999)	3 (Grussu et al., 2007, Ploekinger et al., 1996, Troisi et al., 2002)
Vitamin D	4 (Accortt et al., 2016, Fu et al., 2015, Gur et al., 2014, Robinson et al., 2014)	3 (Fu et al., 2015, Gur et al., 2014, Robinson et al., 2014)
Folate	2 (Blunden et al., 2012, Chong et al., 2014)	1 (Chong et al., 2014)
Vitamin B <sub>12</sub>	2 (Abou-Saleh et al., 1999, Chong et al., 2014)	1 (Abou-Saleh et al., 1999)
Tryptophan	5 <sup>3</sup> (Abou-Saleh et al., 1999, Handley et al., 1977, Handley et al., 1980, Maes et al., 1992, Stein et al., 1976)	4 <sup>3</sup> (Abou-Saleh et al., 1999, Handley et al., 1977, Maes et al., 1992, Stein et al., 1976)
Ferritin	2 (Albacar et al., 2011, Armony-Sivan et al., 2012)	1 (Albacar et al., 2011)

**Abbreviations:** AA = arachidonic acid; AdA = adrenic acid; ALA =  $\alpha$ -linolenic acid; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; LA = linoleic acid; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids.

<sup>1</sup> Number total of studies evaluating the association between the same nutritional biomarker and depression in pregnancy and in the postpartum period reported in at least two included studies.

<sup>2</sup> Number of studies that found any type of significant association (ORs, correlations and regression coefficients) between the same nutritional biomarker and depression.

<sup>3</sup> Maes et al., 1992 reported the Pearson correlation between tryptophan/ (valine, leucine, isoleucine, phenylalanine) and the Zung Depression, Zung Anxiety and State Anxiety Inventory scores at third postnatal day. This ratio between amino acids reflects the availability of tryptophan to the brain.

**Table 5.** Possible future directions emerged from this systematic review

- More studies are needed on nutritional biomarkers and anxiety and psychological stress.
- A single standard tool to assess depression during pregnancy and postpartum.

- More well-designed studies are needed (with adequate statistical power and reporting complete epidemiological association measures, evaluating the same time periods, and reporting data on ethnicity and others important confounder factors).
- Fatty acids levels should be presented in absolute concentrations to allow the comparison between studies.
- Nutritional supplementation should be considered in the study design/data analysis of the studies.
- Longitudinal studies diagnosing psychological distress in more than one point should present number of women and how they were managed in the follow-up.
- More longitudinal studies are needed to evaluate trace elements, amino acids, vitamins, lipids and psychological distress measured over pregnancy and postpartum.
- Women' nutritional status should be reported for micronutrients in studies.

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### Highlights

- Thirty-eight studies were reviewed for associations.
- Serum vitamin D showed an inverse association with pre/postnatal depression.
- Fatty acids and depression and anxiety had divergent or no associations.
- Results are limited by the higher variability across the studies.

